IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:	
TANG, Yiwen	**Art Unit:** 1618
Serial No.: 10/719,516	**Examiner:** Rogers, James William
Filed: 21 November 2003	**Confirmation No.:** 3018
For: COATINGS FOR IMPLANTABLE DEVICES INCLUDING BIOLOGICALLY ERODABLE POLYESTERS AND METHODS OF FABRICATING SAME	

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Dear Sir:

This appeal brief is submitted pursuant to the Notice of Appeal filed 2 November 2009.

REAL PARTY IN INTEREST

The real party in interest is Abbott Cardiovascular Systems, Inc., with its primary place of business at 3200 Lakeside Drive, Santa Clara, California 95054. Abbott Cardiovascular purchased the vascular device division, and all relevant intellectual property including the instant application, of Advanced Cardiovascular Systems, aka Guidant Corporation, in April 2006. The original assignment to Advanced Cardiovascular system was recorded at Reel/Frame 014740/0391 on 21 November 2003.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences that might have any bearing, direct or indirect, on the Board's decision in this appeal.

STATUS OF CLAIMS

The current status of the claims is:

Claims 1-4, 6-8, 11-18, 20, 21, 23-25 and 28-34 are pending and are hereby appealed.

Claims 5, 9, 10, 19, 22, 26, 27, have been canceled.

STATUS OF AMENDMENTS

All amendments have been entered. The claims were last amended as part of an RCE filed on 8 June 2009. Entrance of that submission was acknowledged in the non-final office action mailed on 2 July 2009, from which this appeal is taken.

SUMMARY OF CLAIMED SUBJECT MATTER

This invention is directed to a medical article having a biologically erodible polymeric coating that includes a first polymer having a very low T_g, i.e., less that about -50 °C, and a polymeric additive that is likewise biologically erodible but has a higher T_g

and a greater degree of crystallinity than the first polymer. That is, the claim set consists of two independent claims, claims 1 and 17:

1. A medical article comprising an implantable substrate having a coating, the coating comprising a first biologically erodible polymer having a glass transition temperature below about -50 °C and a biologically erodible polymeric additive mixed with the first polymer, wherein

the polymeric additive has a degree of crystallinity greater than that of the first polymer and has a glass transition temperature of about -50 °C or greater;

the first polymer is selected from poly(esters), poly(caprolactone), poly(4-hydroxybutyrate), poly(3-hydroxyvalerate), poly(3-hydroxybutyrate-co-3-hydroxyvalerate and mixtures thereof; and

the polymeric additive is selected from poly(L-lactide), poly(L-lactide-co-D,L-lactide), poly(glycolide), poly(glycolide-co-L-lactide), poly(caprolactone-co-L-lactide), poly(caprolactone-co-D,L-lactide), copolymers of trimethylene carbonate and mixtures thereof.

Support for the first polymer being biologically erodible and having a T_g below about -50 °C can be found at least at page 10, lines 8-15.

Support for the first polymer being selected from the group consisting of poly(esters), poly(caprolactone), poly(4-hydroxybutyrate), poly(3-hydroxyvalerate), poly(3-hydroxybutyrate-co-3-hydroxyvalerate and mixtures thereof can be found at least at page 5, lines 4-6 and page 10, lines 10-13.

Support for the polymeric additive having a degree of crystallinity greater than that of the first polymer and a T_g of about -50 °C or greater can be found at least at page 10, lines 16-21.

Support for the polymeric additive being selected from the group consisting of poly(L-lactide), poly(L-lactide-co-D,L-lactide), poly(glycolide), poly(glycolide-co-L-

lactide), poly(caprolactone-co-L-lactide), poly(caprolactone-co-D,L-lactide), copolymers of trimethylene carbonate and mixtures thereof can be found at least at page 11, lines 1-13.

17. A method of fabricating a medical article, the method including depositing a coating on at least a portion of an implantable substrate, the coating including a first biologically erodible polymer having a glass transition temperature below about -50 °C and a biologically erodible polymeric additive mixed with the first polymer, wherein:

the polymeric additive has a degree of crystallinity greater than that of the first polymer and has a glass transition temperature of about -50 °C or greater;

the first polymer is selected from poly(esters), poly(caprolactone), poly(4-hydroxybutyrate), poly(3-hydroxyvalerate), poly(3-hydroxybutyrate-co-3-hydroxyvalerate and mixtures thereof; and

the polymeric additive is selected from poly(L-lactide), poly(L-lactide-co-D,L-lactide), poly(glycolide), poly(glycolide-co-L-lactide), poly(caprolactone-co-L-lactide), poly(caprolactone-co-D,L-lactide), copolymers of trimethylene carbonate and mixtures thereof.

Claim 17 is merely a method claim that complements device claim 1. Support for all the elements can be found at least at page 5, lines 19-21 and Examples 1, 2 and 4-7.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds for rejection to be reviewed in this appeal are:

1. Whether claims 1-4, 6-8, 11, 15, 17, 18, 20, 21, 23-25, 28 and 32 are anticipated by Lee, WO 01/21229 (Evidence Appendix, Exhibit "A"), under 35 U.S.C. § 102(b).

2. Whether claims 1-3, 6-8, 11-18, 20, 23-25 and 28-32 are anticipated by Hossainy, EP 0 970 711(Evidence Appendix, Exhibit "B", Hossainy I), under 25 U.S.C. § 102(b).

3. Whether claims 1-3, 6-8, 11, 15, 17, 18, 20, 23-25, 28 and 32-34 are anticipated by DeSimone, et al., US 2004/0181271 (Evidence Appendix, Exhibit "C") under 353 U.S.C. § 102(e).

4. Whether claims 1-3, 6-8, 11, 15, 17, 18, 20, 23-25, 28 and 32-34 are anticipated by Hossainy, et al., US 2001/0014717(Evidence Appendix, Exhibit "D", Hossainy II), under 35 U.S.C. § 102(b).

5. Whether claims 1-3, 6-8, 11-15, 17, 18, 20, 23-25 and 28-34 are unpatentable under 35 U.S.C. § 103 over Hossainy, et al., US 2001/0014717(Evidence Appendix, Exhibit "D", Hossainy II).

6. Whether claims 1-3, 6-8, 11-15, 17, 18, 20, 23-25 and 28-34 are unpatentable under 35 U.S.C. § 103 over DeSimone, US 2004/0181271 (Evidence Appendix, Exhibit "C").

ARGUMENT

In the discussion that follows, appellants' focus will be on the elements of independent claims 1 and 17 since it is well-established that if an independent claim is not anticipated or obvious no claim dependent thereon can be.

Claims 1-4, 6-8, 11, 15, 17, 18, 20, 21, 23-25, 28 and 32 are not anticipated by Lee because each and every element of independent claims 1 and 17 is not disclosed therein.

A rejection based on anticipation requires that all of the claim elements and their limitations be disclosed in a single prior art reference. In other words, anticipation requires that the identical invention be described in the reference. In Re Skvorecz, 580 F.3d 1262 (Fed. Cir. 2009).

The examiner relies on arguments made in an 18 April 2008 office action (Evidence Appendix, Exhibit "E") as the basis for maintaining this rejection. There, the examiner argued that Lee teaches the use of biodegradable polymers including poly(3-hydroxybutyrate-co-3-hydroxyvalerate) , poly(caprolactone) poly(orthoesters),

polyglycolic acids, poly lactic acids and blends and combinations thereof. Next, the examiner points out that the T_g of poly(caprolactone) is -62 °C and exclaims "the claim limitation is considered met." The examiner then forges ahead into a discussion of the first polymer and the polymer additive of the current invention without so much as a nod to the fact that Lee says absolutely, unequivocally and irrefutably nothing about two distinct groups of polymers, a first polymer group and a separate polymeric additive group, the two groups having a very specific physical property relationship to one another. Nor does it appear to bother the examiner that Lee makes no mention whatsoever of T_gs or the crystallinity of the polymers disclosed therein. In fact the sum total of the Lee disclosure regarding polymers is:

> The polymers include chemically synthetic polymers, natural polymers, modified natural polymers, genetically engineered polymers and combinations, copolymer or blends of these compounds. Page 6, lines 10-12.
>
> Biodegradable materials include polyacids, such as poly(3-hydroxybutyrate-co-3-hydroxyvalerate, poly(amino acids), polycaprolactone, poly-epsilon-caprolactone, polyorthoesters, polyesterbased (sic) biodegradable materials ... genetically engineered proteins, genetically engineered polysaccharides, genetically engineered DNAs and RNAs, copolymers, blends and combinations. Page 6, lines 24-29.
>
> If the polymer coating or sheath is used to coat the stent, both biodegradable and non-biodegradable polymers may be used. The polymer is selected depending on the drug selected, the polymer's compatibility with a subject and the ultimate pharmacological effect desired. Page 7, lines 29.

The Lee disclosure listing of applicable polymers covers virtually the entire universe polymers, existing and future. Further, copolymers, blends and combination of every polymer in that universe is disclosed as being within the scope of the invention. From this the examiner, obviously using 110% hindsight, extracts the current invention which is directed to two specific sets of mutually exclusive polymers where the polymers of the second set, the polymeric additives, bears a very specific relationship in terms of physical properties to the polymers of the first set, the "first polymer," as these are set forth in independent claims 1 and 17.

Thus, the possible combinations of polymers based on Lee is almost truly infinite, only a bit less so if the skilled artisan, for no particular reason based on the disclosure of Lee, separates from the vast milieu of disclosed polymers those having the requisite T_gs and degrees of crystallinity. Even then those polymers must be subdivided into two groups, the polymers of one group (the polymeric additives) having a greater degree of crystallinity and a higher T_g than the polymers of the other group (the first polymers). Finally, from these groups, the skilled artisan would still have to divine the specific polymers of the current invention. Simply put, Lee has absolutely no nexus to the current invention.

Claims 1-3, 6-8, 11-18, 20, 23-25 and 28-32 are not anticipated by Hossainy I because each and every element of independent claims 1 and 17 is not disclosed therein.

As is the case with Lee, the examiner stretches the bounds of credulity to find a putative nexus between Hossainy and the current invention. Hossainy, like Lee, attempts to capture virtually the complete realm of polymers, presumably because its invention is not directed toward polymers *per se* but rather toward a method of applying polymeric coatings, which Hossainy would like to be applicable to any polymer. With regard to polymers, Hossainy discloses as useful bioabsorbable polymers in paragraph [0022], biostable polymers in paragraph [0023] and bioabsorbable elastomers, including some specific examples of bioabsorable elastomeric copolymers in paragraph [0025]. The discussion of polymers covers 6 paragraphs comprising some 87 lines of small font text. The only nod to the use of a mixture of two polymers is the inclusion of the obligatory, from a draftspersons point of view, "and combinations thereof" (page 4, line 45), "and blends thereof" (page 4, line 8 and page 5, line 17). Absolutely nothing is said about which polymers to blend with which others. Further, nothing is expressly stated or even suggested regarding T_gs and degrees of crystallinity or the requisite relationship of those properties in one group of polymers to those of another group. The examiner's focus on paragraph [0022] is particularly misleading since all of the polymers in that paragraph are copolymers and none of those is the single copolymer that might comprise the "first polymer" of claims 1 and 17 (Exhibit "E", page 4). Thus, any blend comprising any copolymer of paragraph [0022] would not read on any copolymer of the present invention.

Claims 1-3, 6-8, 11, 15, 17, 18, 20, 23-25, 28 and 32-34 are not anticipated by DeSimone because each and every element of independent claims 1 and 17 is not disclosed therein

DeSimone bears no more relationship to the current invention than do Lee and Hossainy I. DeSimone is concerned with modifying the crystallinity of polymers by annealing them. As for the polymers that can be so treated, DeSimone defines "polymer" and "polymeric material" as being "synonymous [with] and ... broadly construed to include, but not be limited to, homopolymers, copolymers, terpolymers, and the like." (Exhibit "C", paragraph [0027]. In paragraph [0035] DeSimone lists a vast array of polymer families and specific polymers, the crystallinity of which may be modified using the invention therein. DeSimone, however, does not disclose or claim combinations, mixtures, blends, etc. of any polymers. This fact alone removes DeSimone from the scope of the current invention, which requires a blend of polymers from two specific groups, the polymers of one group having a very particular physical property relationship with those of the second group. In addition, DeSimone's only reference to T_gs is to state "An exemplary polymeric material ... according to embodiments of the present invention may have ... a glass transition temperature of between about 60 °C – 65°C" ([Paragraph [0043]). DeSimone does state that its polymeric materials are not limited to that range (Paragraph[0043]) but says nothing whatsoever about what the maximum range can be. Certainly one of skill in the art would be hard-pressed to assume from the DeSimone disclosure that polymers having a T_g less than about minus 50°C (the first polymer of claims 1 and 17) would necessarily be included come within the scope of the invention.

Once again, the examiner has focused on individual polymers in DeSimone and not on the specific blend of polymers having particular physical property relationships of the current invention. As noted previously, the examiner relies on the appearance of words such as "combinations," "mixtures," and "blends" in the references but there is no indication of which polymers to combine, mix or blend.

Claims 1-3, 6-8, 11, 15, 17, 18, 20, 23-25, 28 and 32-34 are not anticipate by Hossainy II because each and every element of independent claims 1 and 17 is not disclosed therein

Hossainy II, like Lee, Hossainy I and DeSimone before, sets forth a gigantic array of polymers in paragraphs [0032] – [0037], [0041] and [0042] that may be used in its invention. Since the list is so extensive it is possible to find a polymer or two of the present invention scattered among them, but Hossainy II offers no direction as to how to select particular polymers so as to anticipate the current invention. In fact, Hossdainy II, like DeSimone, does not even allude to blends of polymers much less how to select which polymers to blend. The examiner once again points to the fact the Hossainy II happens to mention the T_g of poly(caprolactone), which does fall within the range of the first polymer of the current invention, but, as before, the examiner disingenuously ignores entirely the requirement of claims 1 and 17 for a blend of polymers from two groups, all the polymers of the first group having a T_g less than about -50 °C and the all the polymers of the second group having a T_g greater than about -50 °C and a crystallinity greater than that of the selected polymer of the first group. Clearly, Hossainy II has no nexus whatsoever to the claims of the current invention.

Claims 1-3, 6-8, 11-15, 17, 18, 20, 23-25 and 28-34 are patentable over Hossainy II in that the elements of independent claims 1 and 17 are not obvious from the disclosure therein

In the non-final office action mailed 2 July 2009 (Evidence Appendix, Exhibit "F"), from which this appeal is taken, the examiner, after iterating the anticipation rejections over Lee, Hossainy I, DeSimone and Hossainy II, offers up a 35 U.S.C. § 103 obviousness rejection arguing that "Hossainy while describing polymeric blends is silent on specific blend ratios" (Exhibit "F", pages 5-6) but argues that determining such ratios would engender no more than routine optimization.

While appellants do not for a yoctosecond concede that selecting the ratio of polymers comprises nothing more than routine optimization, it is unnecessary to address the point directly because the examiner's argument begins with an egregiously misleading statement. That is, while Hossainy II does mention blends in paragraphs [0010], [0065], [0069], [0071], [0076], [0077] and [0079], polymer blends are described only in paragraphs [0076], [0077] and [0079] and these paragraphs are directed to blends of polyurethanes, blends of cellulosics and blends of polyamides, none of which are among the polymers of either the "first polymer" or the "polymeric additive" of claims

1 and 17". In fact, in paragraph [0078], which relates to polyesters but, significantly, discloses none that is present in claims 1 and 17, there is no mention of blends of polyesters. There is nothing in Hossainy to guide one of ordinary skill in the art to the current invention.

Claims 1-3, 6-8, 11-15, 17, 18, 20, 23-25 and 28-34 are patentable over DeSimone in that the elements of independent claims 1 and 17 are not obvious from the disclosure therein

The examiner reasserts the same argument with regard to obviousness over DeSimone as that discussed above for Hossainy II; that is, while DeSimone does describe polymer blends (according to the examiners), it does not mention specific blend ratios but that would require only routine optimization.

DeSimone in fact makes no mention at all regarding polymer blends, mixtures or combinations. In fact, the only use of any of these words is "mixture," which appears only in paragraphs [0059] and [0066], neither of which pertain to polymer mixtures. Again the examiner attempts to build a case out of thin air. Clearly, without so much as a mention of polymer blends, mixtures and/or combinations, not to mention the requisite characteristics of each polymer in the blend, DeSimone cannot and does not render the current invention obvious.

Miscellanous

Throughout the rejections the examiner attempts to shift the burden to appellants by making the unsupported statement that "same" polymers, which is interpreted to mean polymers composed of the same monomers must have the same physical properties, which is utterly false. That is, those of ordinary skill in the art are fully aware of the fact that the physical properties of polymers, in particular copolymers, will vary substantially depending on the ratio of monomers, the type of polymer, e.g. alternating, random, block, etc., and the conditions under which the polymers are processed. Nowhere is this more in evidence than in DeSimone itself, wherein modification of a physical parameter of the current invention, crystallinity, is disclosed. Further, whether or not the specific characteristics of individual polymers could be assumed to be the same, none of the references cited by the examiner so much as tangentially alludes to the very specific relationship of the polymers of a blend of the current invention, a fact

the examiner conveniently glosses over, in some cases by ignoring the fact that the disclosure of blends in the referenced does not pertain to polymer blends or does not pertain to polymers of the current invention or pertains to blends of absolutely every polymer without any disclosed means of categorizing them in the manner of the current invention.

The examiner also argues that it is up to appellants to include in the claims how polymers having the indicated physical properties can be obtained so as to differentiate them from the prior art where virtually nothing is said regarding physical characteristics. This is simply untrue. The claims state explicitly what the properties of the various polymers must be. Given that goal it would require only routine experimentation by the skilled artisan to prepare polymers having the requisite characteristics. Claims 1 and 17 are complete and state everything necessary to render them unambiguous and plain to the skilled artisan. There can be no "shifting of the burden."

CONCLUSION

The examiner has failed, as a matter of law, to set forth a case of unpatentability of claims 1, 2, 3, 8-10, 13 – 18, 20, 22 and 23 over Webler in view of Chu, claims 12 and 19 over Webler and Chu in further view of Tuch and/or claims 5-7 and 21 over Webler and Chu in view of Gregorich. Appellants therefore respectfully request that the Board reverse the examiner's rejection and order that the application proceed to issue.

Date: 4 January 2010

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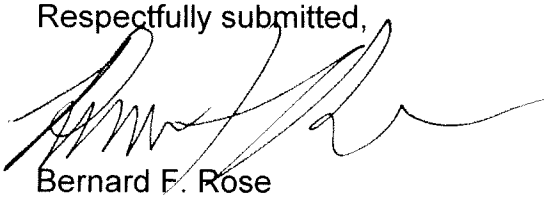
Respectfully submitted,



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CLAIMS APPENDIX

The claims on appeal are:

1. A medical article comprising an implantable substrate having a coating, the coating comprising a first biologically erodable polymer having a glass transition temperature below about –50°C and a biologically erodable polymeric additive mixed with the first polymer,

wherein:

the polymeric additive has a degree of crystallinity greater than that of the first polymer and has a glass transition temperature of about –50°C or greater;

the first polymer is selected from poly(esters), poly(caprolactone), poly(4-hydroxybutyrate), poly(3-hydroxyvalerate), poly(3-hydroxybutyrate-co-3-hydroxyvalerate), and mixtures thereof; and

the polymeric additive is selected from poly(L-lactide), poly(L-lactide-co-D,L-lactide), poly(glycolide), poly(glycolide-co-L-lactide), poly(caprolactone-co-L-lactide), poly(caprolactone-co-D,L-lactide), copolymers of trimethylene carbonate and mixtures thereof.

2. The medical article of Claim 1, wherein the first polymer includes poly(esters).

3. The medical article of Claim 1, wherein the first polymer is poly(caprolactone).

4. The medical article of Claim 1, wherein the first polymer is selected from a group consisting of poly(4-hydroxybutyrate), poly(3-hydroxyvalerate), poly(3-hydroxybutyrate-co-3-hydroxyvalerate), and mixtures thereof.

5. (Canceled)

6. The medical article of Claim 1, wherein the additive is a polymer having the glass transition temperature between about –50°C and about 80°C.

7. The medical article of Claim 1, wherein the additive is a polymer having the glass transition temperature between about –20°C and about 40°C.

8. The medical article of Claim 1, wherein the additive is a polymer having the glass transition temperature between about 0°C and about 20°C.

9-10. (Canceled)

11. The medical article of Claim 1, wherein the medical article is a stent.

12. The medical article of Claim 1, wherein the mass ratio between the first polymer and the polymeric additive is between about 9:1 and about 0.16:1.

13. The medical article of Claim 1, wherein the mass ratio between the first polymer and the polymeric additive is between about 6:1 and about 0.25:1.

14. The medical article of Claim 1, wherein the mass ratio between the first polymer and the polymeric additive is between about 3:1 and about 0.33:1.

15. The medical article of Claim 1, wherein the coating additionally comprises a therapeutic substance.

16. The medical article of Claim 1, wherein the coating is a topcoat layer disposed over a drug reservoir layer for reducing the rate of release of a drug from the reservoir layer.

17. A method for fabricating a medical article, the method including depositing a coating on at least a portion of an implantable substrate, the coating including a first biologically erodable polymer having a glass transition temperature below about –50°C and a biologically erodable polymeric additive mixed with the first polymer, wherein:

the polymeric additive has a degree of crystallinity greater than that of the first polymer and has a glass transition temperature of about –50°C or greater;

the first polymer is selected from poly(esters), poly(caprolactone), poly(4-hydroxybutyrate), poly(3-hydroxyvalerate), poly(3-hydroxybutyrate-co-3-hydroxyvalerate), and mixtures thereof; and

the polymeric additive is selected from poly(L-lactide), poly(L-lactide-co-D,L-lactide), poly(glycolide), poly(glycolide-co-L-lactide), poly(caprolactone-co-L-lactide),

poly(caprolactone-co-D,L-lactide), copolymers of trimethylene carbonate and mixtures thereof.

18. The method of Claim 17, wherein the first polymer includes poly(esters).

19. (Canceled)

20. The method of Claim 17, wherein the first polymer is poly(caprolactone).

21. The method of Claim 17, wherein the first polymer is selected from a group consisting of poly(4-hydroxybutyrate), poly(3-hydroxyvalerate), poly(3-hydroxybutyrate-co-3-hydroxyvalerate), and mixtures thereof.

22. (Canceled)

23. The method of Claim 17, wherein the additive is a polymer having the glass transition temperature between about –50°C and about 80°C.

24. The method of Claim 17, wherein the additive is a polymer having the glass transition temperature between about –20°C and about 40°C.

25. The method of Claim 17, wherein the additive is a polymer having the glass transition temperature between about 0°C and about 20°C.

26-27. (Canceled)

28. The method of Claim 17, wherein the medical article is a stent.

29. The method of Claim 17, wherein the mass ratio between the first polymer and the polymeric additive is between about 9:1 and about 0.16:1.

30. The method of Claim 17, wherein the mass ratio between the first polymer and the polymeric additive is between about 6:1 and about 0.25:1.

31. The method of Claim 17, wherein the mass ratio between the first polymer and the polymeric additive is between about 3:1 and about 0.33:1.

32. The method of Claim 17, wherein the coating additionally comprises a therapeutic substance.

33. The medical article of Claim 1, wherein the polymeric additive comprises poly(L-lactide).

34. The medical article of Claim 17, wherein the polymeric additive comprises poly(L-lactide).

EVIDENCE APPENDIX

Attached hereto are the following Exhibits:

A. WO 01/21229 to Lee, et al.

B. EP 0 970 711 to Hossainy, et al.

C. U.S. 2004/0181271 to DeSimone, et al.

D. U.S. U.S. 2001/0014717 to Hossainy, et al.

E. Non-final Office Action mailed 18 April 2008

F. Non-final Office Action mailed 2 July 2009

EXHIBIT A

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WO 01/21229 A1

(54) Title: ANTIMICROBIAL AND ANTI-INFLAMMATORY ENDOVASCULAR (CARDIOVASCULAR) STENT

(57) Abstract: An antimicrobial and anti-inflammatory endovascular (cardiovascular) stent including base material for the stent and an incorporated antimicrobial agent for the treatment of diseased blood vessel in such way that the antimicrobial agent is slowly released into the disease blood vessel wall which is in direct contact with the stent to treat the blood vessel tissue or the plaque by both killing the disease-causing microbe(s) and relieving the inflammation. The stent can slowly release the antimicrobial and anti-inflammatory agent(s) directly to the diseased tissue or the plaque that is infected by microbes. Consequently, the inflammation is relieved by the anti-inflammatory agent and the inflammation causing microbes are controlled or killed by the antimicrobial agent.

ANTIMICROBIAL AND ANTI-INFLAMMATORY ENDOVASCULAR (CARDIOVASCULAR) STENT

1. Field Of The Invention

The present invention relates to an antimicrobial and anti-inflammatory endovascular (cardiovascular) stent comprising an endovascular (cardiovascular) stent, and an incorporated antimicrobial agent for the treatment of diseased blood vessel in such way that the antimicrobial agent is slowly released into the diseased blood vessel wall which is in direct contact with the stent to treat the blood vessel tissue or the plaque by both killing the disease causing microbe(s) and relieving the inflammation.

More particularly, the present invention relates to an antimicrobial and anti-inflammatory endovascular/cardiovascular stent that slowly releases the antimicrobial and anti-inflammatory agent(s) directly to the diseased tissue or the plaque that is infected by microbes. Consequently, the inflammation is relieved by the anti-inflammatory agent and the inflammation causing microbes are controlled or killed by the antimicrobial agent.

BACKGROUND OF THE INVENTION

Arterial plaques (atherosclerotic plaques or atheromatous lesions) are the thickenings in the coronary arteries. They develop early in life, progressing over a period of many years with phases of quiescence or even regression interspersed with periods of progression. Such coronary atheromatous lesions are commonly found in virtually all adults in the industrialized world although most persons never have signs or symptoms of heart disease. In others, however, atheromatous lesions intrude into the lumen of the coronary arteries and progressively impede blood flow to the myocardium, leading to the clinical syndromes of coronary heart disease.

Balloon angioplasty (i.e., opening up an artery by inflating a balloon advanced across a site of narrowing) is one of the most widely used treatments for heart and vascular disease. However, approximately 33% to 50% of patients treated by balloon angioplasty have renewed narrowing of the treated arteries due to restenosis within six months of the initial procedure. This complication is often serious enough to necessitate further interventions, and stents have increasingly been used to reduce the incidence of restenosis. Notwithstanding, stents often become overgrown by inflammatory restenosis tissue.

Stents are hollow cylindrical devices made of plastic or metal that are inserted into body passageways for the local management of compression, narrowing, or obstruction of the passageway. In the treatment of heart disease, stents are introduced in a narrow collapsed state, guided by a catheter across the blockage, and expanded into place, usually by a balloon to physically hold open the coronary artery. Often, stents allow passage of blood through the previously obstructed artery and can eliminate the need for invasive procedures, such as coronary artery bypass surgery. However, the stents themselves become obstructed due to restenosis 10% to 25 % of the time, less than six months after insertion.

The process of restenosis is partially due to thickening of the blood vessel wall secondary to vascular smooth muscle cell ("VSMC") proliferation, VSMC migration into the inner aspect of the blood vessel wall (intima), and extracellular matrix deposition. There are several interdependent mechanisms which can initiate restenosis and are involved in the final common pathway of the disorder; among the most important being damage to the endothelial lining of the vessel and VSMC changes. Normally endothelium acts as a barrier that separates the blood elements from the remainder of the vessel wall. Consequently, loss or damage to the endothelium, which occurs during angioplasty, atherectomy, or stent insertion, results in a cascade of events that lead to restenosis.

These plaques that occlude coronary arteries are usually associated with infectious microbes, such as *Chlamydia pneumonia* (Jackson IA et al., Am J Pathol 1997 May); *Streptococcus sanguis*; and *Porphyromonas gingivalis* (Herzberg, MC, and Weyer, MW, 150(5):1785-1790); Ann Periodontol 1998 July; 3(1):151-160). The untreated infection of a blood vessel causes localized chronic host tissue inflammation and immune responses at the infected area. Over time, the plaque builds up in bulk and, consequently, constricts the lumen of the blood vessel segment where the chronic infection occurs. In addition to the bacterial agents known to be involved in plaque formation, recent studies indicate that a common virus called *cylomegalovirus* (CMV) may play a role in restenosis. (Zhou YF, Leon MB, Waclawiw MA, et. al., N Eng. J Med. 1996,335:624-30).

Systemic infusion of antibiotic compounds has also been recently suggested as a means to treat atherosclerotic plaques. However, because of the requirement of high dosage over a long treatment period, systemic infusion of antibiotic compounds for the treatment of these plaques may cause many unforeseen adverse effects. This is particularly true in the treatment of CMV, as the compounds most commonly used against this virus, gancyclovir, foscarnet, and combinations thereof are highly toxic and are typically only to be used to treat life threatening infections. Furthermore, development of resistance is common with systemic therapies, such that the drugs become progressively less effective and the disease progresses sooner.

SUMMARY OF THE INVENTION

It is well known that the conventional use of PTCA has very limited, long-term effectiveness to treat atherosclerotic plaques. Approximately 30% of patients have restenosis within 2 to 3 years. By treating the plaque area with indwelling antimicrobial stent(s) after a PTCA (percutaneous transluminal coronary angioplasty) procedure or open-heart procedure, the microbe(s) that has caused the original plaque is destroyed by the antimicrobial agents. Therefore, restenosis (i.e., renarrowing of

the arteries) is prevented. With the presence of an optional anti-inflammatory agent, the inflamed tissue is subdued more rapidly.

In this invention, an antimicrobial and anti-inflammatory vascular stent comprises vascular stent base material; and an incorporated antimicrobial and anti-inflammatory agent for the treatment of diseased blood vessels. It has three functions, i.e., the immediate mechanical support to maintain the patency of the treated blood vessel to allow normal blood flow through the lumen of the diseased blood vessel, the slow release of the antimicrobial agent(s) to kill the infectious microbes, and relieving the inflammation to prevent the renarrowing of the treated blood vessel.

The vascular stent base material can consist of metal alloy, polymer, ceramic or a combination of these materials. The physical form could be a "solid-wall" tube, porous tube, a tube of chick-wire structure, a spring-like coil or a combination thereof. The critical function of the stent is to keep the patency of the blood vessel, i.e. to allow normal or near-normal flow rate of blood at the treatment site of the vessel.

The incorporated antimicrobial agent is released from the stent by dissolution of the agent from the coating or matrix of the stent, hydrolysis and/or enzymatic digestion of the stent material, and a combination of the two mechanisms. The agent can be selected from groups of disinfectants, antiseptics, antibiotics, antimicrobial polymers, and combinations, co-polymers or blends of these compounds.

The device is directly placed in the lumen at the segment of the balloon-dilated blood vessel. Alternatively, it is placed in the lumen of a bypass vessel during a bypass surgery.

DETAILED DESCRIPTION OF THE, INVENTION

The antimicrobial and anti-inflammatory vascular stent of the present invention comprises vascular stent base material; an incorporated antimicrobial agent for the treatment of the narrowing of blood vessels and an incorporated anti-inflammatory agent to subdue the inflamed tissue.

The present invention is superior in many ways to the methods of prior art. The vascular stent on the market is intended to keep the patency of the blood vessel. It does not address the cause of the plaque formation and growth. Because the plaque's growth is not controlled, it can overcome the stent's function at the two ends and/or throughout the stent. That is if the stent is a durable, "solid-wall" tube, the plaque will build up and constrict the blood flow at the ends of the stent. Should the stent be of spring-like coil or "chicken-wire" like structure, the plaque's in-growth between the "wires" will also constrict the blood flow. In all cases, restenosis occurs and the patient will require an open-heart, by-pass surgery.

The antimicrobial vascular and anti-inflammation stent has three functions, i.e., the immediate or long-term mechanical support to maintain the patency of the treated blood vessel to allow normal blood flow through the lumen of the diseased blood vessel; the slow release of an anti-inflammatory agent to subdue the inflamed tissue, and the slow release of the antimicrobial agent(s) to control or kill the infectious microbes residing in the plaque. Because the plaque's growth is stopped, it prevents the future renarrowing of the stented blood vessel.

The antimicrobial vascular stent base material consists of metal, alloy, polymer, ceramic combinations, co-polymers or blends of these compounds. The physical form could be a "solid-wall" tube, a porous tube, a tube-like structure made of chick-wire like material, a spring-like coil, or a combination of them. The critical physical function of the stent is to keep the patency of the blood vessel, i.e. to allow normal or near-normal flow rate of blood at the treatment site of the vessel.

The stent can be constructed out of any of the traditional stent construction materials. Traditional stent materials include metals, alloys, polymers, glasses, ceramics.

The alloys include Nitinol, stainless steel carbide steel and other alloys made of two or more metals. The metals used to manufacture alloys include aluminum,

antimony, beryllium, carbon, cesium, chromium, cobalt, copper, gadolinium, gallium, gold, hafnium, indium, iridium, iron, lead, lithium, magnesium, manganese, molybdenum, nickel, niobium, osmium, palladium, platinum, polonium potassium, rhenium, rhodium, ruthenium, silver, sodium, tantalum, tin, titanium, tungsten, vanadium, yttrium, zinc, and zirconium.

The polymers include chemically synthetic polymers, natural polymers, modified natural polymers, genetically engineered polymers, and combinations, co-polymers or blends of these compounds. Examples of suitable polymers include Teflon, nylon, ethylene vinyl acetate, silicone, polyacenaphthalene, polyacetals, polyacetylene, polyacrylamide, polyacrylates, polyacrylonitrile, poly(alkylene glycols), poly(alkyl methacrylates), polyamic acid, polyamide-imide, polyamides, polybutadiene, polycarbonate, polychloroprene, polyesters, polyethers, polyethylene, polyethylene oxide, polyisobutylene, polyisoprene, polysulfones, polystyrene, poly(methyl methacrylate), poly(olefins), polypropylene, polysulfonamides, polysulfides, polytetrafluoroethylene, polyurethanes, poly(vinyl acetate), poly(vinyl alcohol), poly(vinyl amine), poly(vinylbutyral), poly(vinyl carbazole), poly(vinyl chloride), poly(vinyl fluoride), poly(vinyl formal), poly(vinylidene chloride), poly(vinyl isobutyl ether) poly(4-vinyl pyridine), poly(vinyl pyrrolidine), poly(vinyl stearate), copolymers, blends and combinations.

Biodegradable materials include polyacids, such as poly(3-hydroxybutyrate-3-hydroxyvalerate), poly (amino acids), polycaprolactone, poly-epsilon-caprolactone, polyesterbased biodegradable materials, poly(aminocaproic acid), polyanhydrides, polyorthoesters, polypeptides, such as polylysine, polyglycolic acids, polylactic acids, genetically engineered proteins, genetically engineered polysaccharides, genetically engineered DNAs and RNAS, copolymers, blends and combinations.

The ceramics include glass ceramics, ceramics made of base metals in the chemical compositions of borides, carbides, nitrides, oxides, and silicides, and

combinations, or blends of these compounds. The incorporated antimicrobial agent is released from the stent base material by dissolution of the agent from the coating or matrix of the stent material hydrolysis and/or enzymatic digestion of the stent material and a combination of the two mechanisms. The antimicrobial agents include disinfectants, antiseptics, antibiotics, antimicrobial polymers, and combinations, co-polymers or blends of these compounds.

The stent material may be coated with the pharmacologic compounds either directly or the compounds may be incorporated into a polymer coating on the stent material. Local delivery of drug(s) using stents is known by three methods: (1) directly coating the stent wires with a drug or a drug-polymer combination (Bailey et al., Circulation 82:III-541 (1990); Cavendar et al., Circulation 82:III-541 (1990)); (2) incorporating a drug into a stent that was constructed not of metal but of a biodegradable polymer (Murphy et al., J. Invasive Cardiol. 3:144-148 (1991)); and (3) a polymer sheath around the stent (U.S. Patent No. 5,383,928). Most investigators and stent companies have focused their efforts on directly coating the metal stent wires with a polymer. This polymer is usually placed directly on the stent (e.g., by dipping the stent in soluble polymer) or is covalently bound to the metal. The polymer is bonded to or contains the effective compound. Most coated stents currently under development use the anticoagulant, heparin, as their active agent. One of the more effective polymer coatings for stents is Biogold (van der Giessen et al., Circulation 82: III-542 (1990)).

If a polymer coating or sheath is used to coat the stent, both biodegradable and non-degradable polymers may be used. The polymer is selected depending on the drug selected, the polymer's compatibility with a subject and the ultimate pharmacologic effect desired. For example, if the effect need only last a short period, a thin polymer can be used with a limited amount of drug capable of diffusing from the polymer into the arterial wall or lumen. Alternatively, only the layer closest to the

body fluid would contain the drug. Another alternative would be to use a polymer that is biodegradable over a short period of time. Naturally, the opposite characteristics would be selected for a desired prolonged release. The characteristics of the particular polymer for these purposes is well known to the skilled artisan or can be determined by reference to standard references, e.g., Biodegradable Polymers as Drug Delivery Systems, R. Langer and M. Chasin, Eds., Marcel Dekker Inc., New York, N.Y., USA (1990); Engleberg and Kohn, "Physico-mechanical properties of degradable polymers used in medical applications: a comparative study," Biomaterials 12:292-304 (1991); Controlled Release Delivery Systems, T. J. Roseman and S. D. Mansdorf, Eds., Marcel Dekker Inc., New York, N.Y., USA (1983); and "Controlled Release Technology, Pharmaceutical Applications, ACS Symposium Series, Vol. 348, P. I. Lee and W. R. Good, Eds., American Chemical Society, Washington, D.C., USA (1987). Furthermore, a polymer may be chosen so that the breakdown products of the polymer have either an antimicrobial or an anti-inflammatory effect.

Antimicrobial agents are selective inhibitors of DNA, protein and cell wall metabolic pathways unique to susceptible organisms. Therapeutic success is achieved when the drug favorably affects the balance between microbial virulence and host resistance. This will occur if the drug is active against the infecting organism; an effective drug level is achieved at the site of infection; and host resistance is not compromised.

Effective prescription of antimicrobial therapy requires an accurate diagnosis and a decision on the need for antimicrobial therapy. An empirical assessment of likely invective organisms (based on the site and severity of infection, the patient's immunocompetence and a knowledge of local infection patterns) should be followed by a microbiological diagnosis and sensitivity testing whenever possible. Furthermore, many infections do not require, or are not susceptible to, specific

antimicrobial therapy. Unnecessary therapy is expensive and may result in adverse drug reactions and contribute to the problem of antibiotic resistance.

The choice of antimicrobial agent is based on known or likely invective organisms, site of infection, the immune status of the patient and renal and hepatic function. Single drug therapy using a narrow-spectrum agent is optimal and carries the least risk of superinfection and development of resistance. The use of multiple antibiotics is indicated only for short-term, empiric, broad-spectrum cover for serious infections or to minimize the risk of development of antibiotic resistance during therapy.

The antimicrobial compound is selected from the group consisting of antibacterial compounds, antifungal compounds, antiviral compounds, and antiprotozoal compounds.

Antibacterial compounds are those compounds which are destructive to or prevent the growth of bacteria. Both synthetic and antibiotic antibacterial compounds are suitable for use in the present invention. By antibiotic it is meant to include soluble substances derived from a mold or bacteria that inhibit or prevent the growth of other microorganisms. By synthetic, it is meant those antibacterial compounds artificially synthesized, rather than extracted or derived from a mold or bacteria.

Suitable antibiotic antibacterial compounds include aminoglycosides, amphenicols, ansamycins, ß-Lactams, lincosamides, macrolides, polypeptides, and tetracyclines. While not fitting neatly into one of the above classifications, other antibiotic antibacterial compounds such as cycloserine, mupirocin, and tuberin may also be suitable for use in the present invention.

Aminoglycosides are antibiotics whose structure contains amino sugars attached to an aminocyclitol ring (hexose nucleus) by glycosidic bonds. Aminoglycoside antibiotics are derived from various species of *streptomycin* and

micromonospora or are produced synthetically. They act by inhibiting protein synthesis, chiefly by binding to the 30S ribosomal subunits.

Amphenicols are broad-spectrum, mainly bacteriostatic antibiotics, active against a wide range of Gram-negative bacilli (but not *Pseudomonas),* staphylococci, streptococci, *Haemophilus* species, anaerobes and rickettsia, but ineffective against chlamydia and mycoplasma. Because of their potential to cause a plastic anemia, they should be reserved for severe infections caused by susceptible organisms.

ß-lactam compounds contain a four-membered ring with an amide nitrogen and a keto group. This configuration includes bacteriostatic, cell-wall inhibiting antibiotics, such as penicillins and cephalosporins; their analogs and derivatives, such as the penmen (or penman) compounds; clavulanic acids; ß-lactams; carbacephems; carbapenems; cephamycins; and monobactams. They are substrates for and may act as inhibitors of bacterial beta-lactamases.

Carbapenems comprise a group of ß-lactam antibiotics in which the sulfur atom in the thiazolidine ring of the penicillin molecule is replaced by a carbon atom. Thienamycins are a subgroup of carbapenems which have a sulfur atom as the first constituent of the side chain.

Cephalosporins are a group of broad-spectrum antibiotics first isolated from the Mediterranean fungus acremonium (*cephalosporium acremonium*). They contain the ß-lactam moiety thia-azabicyclo-octenecarboxylic acid, also called 7-aminocephalosporanic acid.

Cepbamycins are a naturally produced family of ß-lactam cephalosporin-type antibiotics having a 7-methoxy group and possessing marked resistance to the action of ß-lactamases from gram-positive and gram-negative organisms.

Lincosamides include clindamycin and lincomycin. Clindamycin is a derivative of lincomycin, but is more potent. Its mechanism of action is similar to that

of erythromycin: it binds to the 50S ribosomal subunits, selectively inhibiting bacterial protein synthesis.

Macrolides are a group of antibiotics containing a macrocyclic lactone ring linked glycosidically to one or more sugar moieties. These antibiotics are produced by certain species of *streptomyces*. They often inhibit protein synthesis by binding to the 50s subunits of 70s ribosomes.

Polypepide antibiotics are those antibiotics whose structure contains one or more peptides, usually cyclic. They are generally effective against gram-positive bacteria and act by inhibiting peptidoglycan synthesis in bacterial cell walls.

Glycopeptide antibiotics are those antibiotics whose structure contains one or more cyclic peptides to which are attached one or more deoxy sugars in glycosidic linkage. They are generally effective against gram-positive bacteria and act by inhibiting peptidoglycan synthesis in bacterial cell walls. An example of a glycopeptide antibiotic is vancomycin.

Tetracycline antibiotics are broad-spectrum natural and semisynthetic antibiotics with a naphthalene structure obtained from various *streptomyces* species. The tetracyclines are predominantly bacteriostatic agents that inhibit bacterial protein synthesis by binding to 30S ribosomal subunits in susceptible organisms. With the exception of doxycycline and minocycline, tetracyclines inhibit protein synthesis from amino acids in the patient, an antianabolic effect reflected by raised blood urea levels. Thus, localized delivery by the stent of the present invention, rather than systemic administration, would be beneficial if and when tetracycline use is indicated.

Synthetic antibacterial compounds include diaminopyrimidines; nitrofurans; quinolones and their analogs; sulfonamides; and sulfones.

2-4-diaminopyrimidines, such as trimetboprim, act by blocking the action of bacterial dihydrofolate reductase which leads to inhibition of folate synthesis in susceptible microorganisms. Trimethoprim is increasingly being used on its own and

its efficacy compares well with that of co-trimoxazole, with the advantage of fewer adverse effects.

Nitrofurans are generally effective against both gram-positive and gram-negative bacteria. Examples include nitrofurazone and nitrofurantoin. Nitrofurantoin is widely used for long term suppression of bacterial growth.

Quinolones, such as the fluoroquinolones, are bactericidal and act by inhibiting DNA gyrase, interfering with reproduction of bacterial DNA.

The sulphonamides are usually bacteriostatic and arrest cell growth by inhibiting bacterial folic acid synthesis. They are effective against sensitive strains of gram-negative and gram-positive bacteria *Actinomyces, Nocardia and Plasmodia.* However, extensive clinical use over many years has resulted in a high level of resistance and current use is limited.

Antifungal compounds are those compounds which are antagonistic to fungi. They can either be fungistatic (growth-inhibiting) or fungicidal (destructive action). Both synthetic and antibiotic antifungal compounds are suitable for use in the present invention.

Suitable antibiotic antifungal compounds are typically polyenes. Additionally, while not fitting neatly into any given category, other antifungal compounds such as azaserine; griseofulvin; oligomycins; neomycin undecylenate; pyrrolnitrin; siccanin; tuberculin; and viridin may be suitable for use in the present invention.

The most commonly used polyene antifugal compound is Amphotericin B.

Synthetic antifungal compound, include allylamines; imidazoles; thiocarbamates; and triazoles. While not fitting neatly into any of the above classifications, additional suitable synthetic antifungal compounds also include acrisorcin; amorolfine; biphenamine; bromosalicylchoranilide; buclosamide; calcium propionate; chlorphenesin; ciclopirox; cloxyquin; coparaffinate; diamthazole dihydrochloride; exalamide; flucytosine; halethazole; hexetidine; loflucarban;

niufuratel; potassium iodide; propionic acid; pyrithione; salicylanilide; sodium propionate; sulbentine; tenonitrozole; triacetin; ujothion; undecylenic acid; and zinc propionate.

The azole derivatives suitable for use in this invention include the imidazoles (e.g., ketoconazole and miconazole) and the triazoles (e.g., itraconazole and fluconazole). They have a broad spectrum of activity against several dermatophytes, *Candida, Cryptococcus* and other fungi that cause deep-seated infections. The mechanism of action involves inhibition of the cytochrome P450 enzyme responsible for conversion of lanosterol to ergosterol, the major sterol of most fungal cell membranes. The drugs' affinity is, however, not specific for fungal cytochrome P450; there is cross-reactivity with mammalian P450 enzymes and this explains the potential interference with human steroid synthesis and the interaction with other hepatically metabolized drugs. They have a broad antimycotic spectrum of activity and vary in their cidal and static effects.

Antiviral compounds are compounds which are destructive to a virus or otherwise weaken or abolish its action. The most commonly used antiviral compounds are the nucleoside analogues. Additional suitable antiviral compounds include acemannan; acetylleucine monoethanolamine; amantadine; amidinomycin; delavirdine; foscarnet sodium; indinavir; interferon-α; interferon-ß; interferon-γ; kethoxal; lysozyme; methisazone; moroxydine; nevirapine; podophyllotoxin; ribavirin; rimantadine; ritonavir; squinavir; stallimycin; statolon; tromantadine; and xenazoic acid.

The nucleoside analogues either interfere with DNA synthesis of viruses (acyclovir, ganciclovir, and cidofovir), or they inhibit reverse transcriptase of retroviruses (zidovudine and didanosine). Acyclovir, guanosine analogue, is phosphorylated to the active triphosphate form after uptake into the cell. Thymidine kinase catalyses the initial phosphorylation; selective toxicity in infected cells is due

to the greater affinity of the drug for viral, compared with host, thymidine kinase. Acyclovir triphosphate inhibits viral DNA polymerase, and it also competes with cellular deoxyguanosine triphosphate for incorporation into the viral DNA, thus terminating viral DNA systhesis. Ganciclovir, a guanine analogue, is active in the triphosphate form to which it is converted in the host cell. Ganciclovir triphosphate is a selective inhibitor of viral DNA polymerase and it competes with deoxyguanosine triphosphate for incorporation into DNA, causing chain termination. Ganciclovir triphosphate is concentrated in CMV-infected cells to a level ten-fold that in uninfected cells. In vitro activity against CMV is 100-fold greater than that of acyclovir, and against Epstein-Barr virus (EBV), 10-fold greater. Activity against herpes simplex and varicella-zoster is equivalent to acyclovir. Systemic use of ganciclovir is limited by toxicity. Cidofavir is a nucleotide analogue that also inhibits DNA polymerase activity. Its long intracellular half-life may lend itself well to slow delivery via impregnated stent.

Foscarnet sodium (syn. Trisodium phosphonoformate) is an inorganic pyrophosphate analogue that causes selective inhibition of viral DNA polymerase and reverse transcriptase, with little effect on host cell enzymes.

If the restinosis-inducing microbe is suspected to be cytomegalovirus (CMV) the preferred antiviral compounds are ganciclovir, cidofovir, and foscarnet sodium.

Antiprotozal compounds are compounds which are destructive to a protozoa or otherwise weaken or abolish its action. Suitable antiprotozal compounds include those compounds having action against ameba, giardia, histomonas, leishmania, malaria, pneumocystis, toxoplasma, trichomonas, and trypanosoma.

The stent of the present invention is preferably further impregnated or otherwise treated with an anti-inflammatory compound. The anti-inflammatory compound assists in the prevention of restinosis by reduction of inflammation at the site of infection. Anti-inflammatory compounds are those compounds which reduce

inflammation by acting on body mechanism without directly antagonizing the causative agent; and are generally divided into two main groups, non-steroidal and steroidal.

Nonsteroidal anti-inflammatory compounds include aminoarylcarboxylic acid derivatives; arylacetic acid derivatives; arylbutyric acid derivatives; arylcarboxylic acids; arylpropionic acid derivative; (e.g., naproxen); pyrazoles; pyrazolones; salicylic acid derivatives (e.g., aspirin); and thiazinecarboxamides. While not fitting neatly into any of the above categories, other anti-inflammatory compounds such as ε-acetamidocaproic acid; s-adenosylmethionine; 3-amino-4-hydroxybutyric acid; amixetrine; bendazac; benzydamine; α-bisabolol; bucolome; difenpiramide; ditazol; emorfazone; fepradinol; guaiazulene; nabumetone; nimesulide; oxaceprol; paranuline; perisoxal; proquazone; superoxide dismutase; tenidap; and zileuton may be suitable for use in the present invention.

The therapeutic properties of all the non-steroidal anti-inflammatory agents (NSAIDs) are characteristic of the prototype, aspirin, namely: analgesic, antipyretic and anti-inflammatory, the latter providing the potential for greater symptomatic relief in pain and discomfort associated with inflammation. Most of the actions of NSAIDs are probably attributable to their ability to inhibit cyclo-oxygenase, the enzyme responsible for prostaglandin synthesis. NSAIDs other than aspirin have these major properties at usual therapeutic doses, whereas high doses of aspirin (which may be poorly tolerated) are needed for significant anti-inflammatory effect. However, aspirin may have considerable cost advantage over the other NSAIDs.

In choosing NSAIDs, several factors must be considered. The differences in tolerability and efficacy among the various NSAIDs available are sometimes considerable, but the major factor influencing choice of agent is likely to be the wide variation in individual patient response-- many patients not responding to, or intolerant of, one drug may well benefit from another. The main differences among

the NSAIDs are pharmacokinetic and in the incidence and type of unwanted effects. The elimination half-lives vary widely, being the longest for piroxicam (37-86 hours) and tenoxicam (42-78 hours). All the NSAIDs have been associated with dermatological, gastrointestinal, renal, hepatic, hematological and immunological adverse effects, but differences may be largely determined by individual susceptibility. Patients who are pseudoallergic to a particular NSAID are prone to exhibit cross-reactivity to other NSAIDs, including aspirin (and possibly to tartrazine). The concurrent administration of different NSAIDs is not advised, on pharmacokinetic and efficacy/toxicity grounds.

Steroidal anti-inflammatory compounds are glucocorticoids, steroid-like compounds capable of significantly affecting intermediary metabolism. Examples include cortisone; hydrocortisone; and prednisone.

After the dilation of the blood vessel segment with PTCA procedure, the device is directly placed in the lumen of the diseased segment of the blood vessel.

PREPARATION OF COMPOSITION

The following specific examples will illustrate several embodiments of the present invention. It will be appreciated that other examples will be apparent to those of ordinary skill in the art and that the invention is not limited to these specific illustrative examples.

EXAMPLE 1

A sterile, surgical steel, endovascular (cardiovascular) stent is aseptically dipped into a sterile solution of 20% benzalkonium chloride, 5% hydrocortisone, and 75% ethanol solution. Then the coated device is aseptically air dried for 30 minutes at room temperature. The finished product is aseptically packaged and ready to be shipped to hospital.

EXAMPLE 2

An endovascular (cardiovascular) stent is made of 1% hydrocortisone and 99% tributyltin methacrylate-methyl methacrylate polymer by injection molding. Then it is packaged and sterilized using 1.0 MRAD gamma-radiation. After placing it inside the blood vessel, the polymer that is slowly hydrolyzed releases antimicrobial $ClSnBu_3$ molecules into the contacting plaque to kill infectious microbes.

EXAMPLE 3

Compound 98% polylactide, 1% 5-fluorocytosin and 0.1% trisamcinolone is extruded through a 100 micron die into a coil form with a 5-mm O.D. The coil is then cut into various lengths, such as 5, 10, 15 mm. After balloon dilation per PTCA procedure, a 10-mm long coil is chosen and placed in the treated vessel. The anti-microbial agent is slowly released from the stent as polylactide is gradually hydrolyzed over a period of 2 to 4 months.

EXAMPLE 4

A commercially available sterile endovascular (cardiovascular) stent is aseptically dipped into a solution of 50% Tecoflex, 45% THF and 5% nalidixic acid. The coated stent that is then aseptically dried in sterile air is packaged for either inventory or for shipment to hospital. The finished product is used to keep the treated blood vessel patent according to manufacturer's instruction for use.

What is claimed is:

1. An endovascular (cardiovascular) stent comprising:

(a) stent material; and

(b) an antimicrobial agent.

2. The stent of Claim 1 wherein the stent material is selected from the group consisting of polymers, metals, ceramics, shape-memory materials, bio-polymers, bio-degradable materials, combinations, blends and composites.

3. The stent of Claim 1 wherein the antimicrobial agent is covalently or ionically linked to the stent material, physically trapped throughout the stent, in a coating on the surface of the stent, and/or in the form of a base unit of a polymeric stent material.

4. The stent of Claim 1 wherein the antimicrobial agent is selected from the group consisting of anti-bacterial agents, anti-fungal agents, anti-viral agents, and combinations thereof.

5. The stent of Claim 1, further comprising an anti-inflammatory agent.

6. The stent of Claim 5, wherein said anti-inflammatory agent is covalently or ionically linked to the stent material, physically trapped throughout the stent, in a coating on the surface of the stent, and/or in the form of a base unit of a polymeric stent material.

7. The stent of Claim 5, wherein said anti-inflammatory agent is selected from the group consisting of anti-inflammatory enzymes, salicylates, steroids, sulfonamides, anti-viral agents, and anti-metabolites, and combinations thereof.

8. The stent of Claim 2 wherein the polymers or plastics include Teflon, nylon, ethylene vinyl acetate, silicone, polyacenaphthalene, polyacetals, polyacetylene, polyacrylamide, polyacrylates, polyacrylonitrile, poly(alkylene glycols), poly(alkyl methacrylates), polyamic acid, polyamide-imide, polyamides, polybutadiene, polycarbonate, polychloroprene, polyesters, polyethers, polyethylene,

polyethylene oxide, polyisobutylene, polyisoprene, polysulfones, polystyrene, poly(methyl methacrylate), poly(olefins), polypropylene, polysulfonamides, polysulfides, polytetrafluoroethylene, polyurethanes, poly(vinyl acetate), poly(vinyl alcohol), poly(vinylbutyral), poly(vinyl carbazole,) poly(vinyl chloride), poly(vinyl fluoride), poly(vinyl formal), poly(vinylidene chloride), poly(vinyl isobutyl ether) poly(4-vinyl pyridine), poly(vinyl pyrrolidone), poly(vinyl stearate), copolymers, blends and combinations thereof.

9. The stent of Claim 2 wherein the metals include aluminum, antimony, beryllium, carbon, cesium, chromium, cobalt, copper, gadolinium, gallium, gold, hafnium, indium, iridium, iron, lead, lithium, magnesium, manganese, molybdenum, nickel, niobium, osmium, palladium platinum, polonium, potassium, rhenium, rhodium ruthenium, silver, sodium, tantalum, tin, titanium, tungsten, vanadium, yttrium, zinc, zirconium and their alloys.

10. The stent of Claim 2 wherein the ceramics are selected from groups of borides, carbides, nitrides, oxides, and silicides and glass ceramics including glass and calcium phosphate-based materials.

11. The stent of Claim 2 wherein the shape-memory materials include Nitimol, a shape-memory nickel titanium alloy.

12. The stent of Claim 2 wherein the biopolymers include polysaccharides, mucopolysaccharides, proteins, lipids, polynucleotides, co-polymers, combinations, and blends.

13. The stent of Claim 2 wherein the biodegradable materials include polyacids, such as poly(3-hydroxybutyrate-3-hydroxyvalerate), poly (amino acids), polycaprolactone, poly-epsilon-caprolactone, polyester-based biodegradable materials, poly(aminocaproic acid), polyanhydrides, polyorthoesters, polypepides, such as polylysine, polyglycolic acids, polylactic acids, genetically engineered proteins,

genetically engineered polysaccharides, genetically engineered DNAs and RNAs, copolymers, blends and combinations thereof.

14. A method of treating atherosclerotic plaques and atheromatous lesions using an endovascular (cardiovascular) stent comprising:

a) stent material; and

b) an antimicrobial agent.

15. The stent of Claim 14 wherein the stent material is selected from the group consisting of polymers, metals, ceramics, shape-memory materials, bio-polymers, bio-degradable materials, combinations, blends and composites.

16. The stent of Claim 14 wherein the antimicrobial agent is covalently or ionically linked to the stent material, physically trapped throughout the stent, in a coating on the surface of the stent, and/or in the form of a base unit of a polymeric stent material.

17. The stent of Claim 14 wherein the antimicrobial agent is selected from the group consisting of anti-bacterial agents, anti-fungal agents, anti-viral agents, and combinations thereof.

18. The stent of Claim 14, further comprising an anti-inflammatory agent.

19. The stent of Claim 18, wherein said anti-inflammatory agent is covalently or ionically linked to the stent material, physically trapped throughout the stent, in a coating on the surface of the stent, and/or in the form of a base unit of a polymeric stent material.

20. The stent of Claim 18, wherein said anti-inflammatory agent is selected from the group consisting of anti-inflammatory enzymes, salicylates, steroids, sulfonamides, anti-viral agents, and anti-metabolites, and combinations thereof.

21. The stent of Claim 15 wherein the polymers or plastics include Teflon, nylon, ethylene vinyl acetate, silicone, polyacenaphthalene, polyacetals, polyacetylene, polyacrylamide, polyacrylates, polyacrylonitrile, poly(alkylene

glycols), poly(alkyl methacrylates), polyamic acid, polyamide-imide, polyamides, polybutadiene, polycarbonate, polychloroprene, polyesters, polyethers, polyethylene, polyethylene oxide, polyisobutylene, polyisoprene, polysulfones, polystyrene, poly(methyl methacrylate), poly(olefins), polypropylene, polysulfonamides, polysulfides, polytetrafluoroethylene, polyurethanes, poly(vinyl acetate), poly(vinyl alcohol), poly(vinylbutyral), poly(vinyl carbazole,) poly(vinyl chloride), poly(vinyl fluoride), poly(vinyl formal), poly(vinylidene chloride), poly(vinyl isobutyl ether) poly(4-vinyl pyridine), poly(vinyl pyrrolidone), poly(vinyl stearate), copolymers, blends and combinations thereof.

22. The stent of Claim 15 wherein the metals include aluminum, antimony, beryllium, carbon, cesium, chromium, cobalt, copper, gadolinium, gallium, gold, hafnium, indium, iridium, iron, lead, lithium, magnesium, manganese, molybdenum, nickel, niobium, osmium, palladium, platinum, polonium, potassium, rhenium, rhodium ruthenium, silver, sodium, tantalum, tin, titanium, tungsten, vanadium, yttrium, zinc, zirconium and their alloys.

23. The stent of Claim 15 wherein the ceramics are selected from groups of borides, carbides, nitrides, oxides, and silicides and glass ceramics including glass and calcium phosphate-based materials.

24. The stent of Claim 15 wherein the shape-memory materials include Nitimol, a shape-memory nickel titanium alloy.

25. The stent of Claim 15 wherein the biopolymers include polysaccharides, mucopolysaccharides, proteins, lipids, polynucleotides, co-polymers, combinations, and blends.

26. The stent of Claim 15 wherein the biodegradable materials include polyacids, such as poly(3-hydroxybutyrate-3-hydroxyvalerate), poly (amino acids), polycaprolactone, poly-epsilon-caprolactone, polyester-based biodegradable materials, poly(aminocaproic acid), polyanhydrides, polyorthoesters, polypepides, such as

polylysine, polyglycolic acids, polylactic acids, genetically engineered proteins, genetically engineered polysaccharides, genetically engineered DNAs and RNAs, copolymers, blends and combinations thereof.

INTERNATIONAL SEARCH REPORT

In tional Application No
PCT/US 00/40979

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L31/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 90 13332 A (CEDARS SINAI MEDICAL CENTER) 15 November 1990 (1990-11-15) page 5, line 10 -page 6, line 5 claims 1-3,5	1-22
X	US 5 869 127 A (ZHONG SHENG-PING) 9 February 1999 (1999-02-09) abstract column 7, line 18 - line 34 column 9, line 12 - line 23	1-3,5,6, 8-11, 14-16, 18,19, 21-24
A	WO 91 12779 A (MEDTRONIC INC) 5 September 1991 (1991-09-05) page 7, line 17 -page 10, line 18	1-3,5-7, 14-16, 18-20

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 January 2001	08/02/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Heck, G

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/40979

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 762 638 A (DOMB ABRAHAM J ET AL) 9 June 1998 (1998-06-09) column 1, line 15 - line 31 column 5, line 63 -column 6, line 32	1,5,14, 18

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 14-26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte tional Application No
PCT/US 00/40979

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9013332 A	15-11-1990	US 4923415 A	08-05-1990
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		AU 3733097 A	10-02-1999

EXHIBIT B

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 970 711 A2

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(54) **Process for coating stents**

(57) A process is provided for coating stents having a first and second surface with passages there between to avoid blockage and bridging of the passages. The process comprises contacting the stent with a liquid coating solution containing a film forming biocompatible polymer under conditions suitable to allow the film forming biocompatible polymer to coat at least one surface of the stent while maintaining a fluid flow through said passages sufficient prevent the film forming biocompatible polymer from substantially blocking said passages. Also described are stents coated by this process.

EP 0 970 711 A2

Description

Field of the Invention

[0001] This application claims benefit from U.S. Provisional Application No. 60/91,217 filed June 30, 1998, which is hereby incorporated by reference herein. The invention relates generally to a process for coating surgical devices. More specifically this invention relates to an improved process for coating stents and the like.

Background of the Invention

[0002] Stents, which are generally open tubular structures, have become increasingly important in medical procedures to restore the function of body lumens. Stents are now commonly used in translumenial procedures such as angioplasty to restore an adequate blood flow to the heart. However, stents may stimulate foreign body reactions that result in thrombosis or restenosis. To avoid these complications a variety of stent coatings and compositions have been proposed in the literature both to reduce the incidence of these complications or other complications and restore tissue function by itself or by delivering therapeutic compound to the lumen.

[0003] Stents generally are coated by simple dip or spray coating of the stent with polymer or polymer and a pharmaceutical/therapeutic agent or drug. These methods are acceptable for early stent designs that were of open construction fabricated from wires (Wiktor stent) or from ribbons (Gianturco). Dip coating with relatively low coating weights (about 4% polymer) could successfully coat such stents without any problems such as excess coating bridging (i.e. forming a film across) the open space between structural members of the device. This bridging is of particular concern when coating more modern stents that are of less open construction, such as the Palmaz-Schatz, Crown, Multilink or GFX stents. Bridging of the open space (slots) is undesirable because it can interfere with the mechanical performance of the stent, such as expansion during deployment in a vessel lumen. Bridges may rupture upon expansion and provide sites that activate platelet deposition by creating flow disturbances in the adjacent hemodynamic environment or pieces of the bridging film may break off and cause further complications. Bridging of the open slots may also prevent endothelial cell migration complicating the endothelial cell encapsulation of the stent.

[0004] Similarly, spray coating can be problematic in that there is a significant amount of spray lost during the process and many of the pharmaceutical agents that one would like to incorporate in the device are quite costly. In addition, in some cases it would be desirable to provide coated stents with high levels of coating and drug. High concentration coatings (-15% polymer with additional drug) are the preferred means to achieve high drug loading. Multiple dip-coating has been described in the literature as a means to build thicker coatings on the stent. However, composition and phase dispersion of the pharmaceutical agents affect sustained release. In addition, the application of multiple dip coats from low concentration solutions often has the effect of reaching a limiting loading level as an equilibrium is reached between the solution concentration and the amount of coating, with or without pharmaceutical agent, deposited on the stent.

Summary of the Invention

[0005] We have discovered a process for coating stents that avoids bridging and allows for preferential coating of stent surfaces. The process comprises contacting a stent having a first and second surface with passages there between with a liquid coating solution containing a film forming biocompatible polymer under conditions suitable to allow the film forming biocompatible polymer to coat at least one surface of the stent while maintaining a fluid flow through said passages sufficient to prevent the film forming biocompatible polymer from substantially blocking said passages.

[0006] In a preferred embodiment of the present invention the coating process would comprise placing a tubular stent having a first and second surface with passages there between on a mandrel and contacting the stent and mandrel with a liquid coating solution containing a film forming biocompatible polymer under conditions suitable to allow the film forming biocompatible polymer to coat at least one surface of the stent while moving the stent relative to the mandrel to cause fluid flow through said passages sufficient to prevent the film forming biocompatible polymer from substantially blocking said passages.

[0007] In another embodiment of the present invention there is provided a coated stent, comprising a tubular stent having a first and second surface with passages there between, coated with a film-forming biocompatible polymer wherein the polymer coating is greater than 0.5 percent by weight of the coated stent and the passages are not substantially blocked by the bridging of the polymer coating.

Brief Description of the Figures

[0008] Figure 1 illustrates a perspective view of a stent prior to coating.

[0009] Figure 2 is a perspective view that illustrates the placement of a stent on a mandrel prior to coating.

[0010] Figure 3 illustrates the movement of the stent relative to the mandrel in the after removal from the coating bath during the coating process.

[0011] Figure 4 is an enlarged view of a portion of the coated stent that illustrates the substantial absence of bridging of the stent slots or passages.

[0012] Figure 5 is a pictomicrograph that illustrates a stent that has been coated by conventional dip coating process with about a 4 weight percent coating solution.

[0013] Figure 6 is a pictomicrograph that illustrate a stent that has been coated by the inventive coating process with about a 13 weight percent coating solution.

[0014] Figure 7 is a graphical illustration of the in vitro release profile of a coated stent.

[0015] Figure 8 is a graphical illustration of the in vivo release profile of a coated stent.

Detailed Description

[0016] The present invention provides a process for coating medical devices. The process described herein is well suited to coating medical devices that have passages that may otherwise be blocked or have bridges formed by conventional dip coating. As previously discussed avoiding the formation of bridges is especially important in the coating of perforated structures such as stents. Bridging is a significant problem with stents with passages with a minor dimension less than about 125 mils, especially with passages having a minor dimension smaller than about 50 mils.

[0017] Stents are generally cylindrical and perforated with passages that are slots, ovoid, circular or the like shape. Stents may also be composed of helically wound or serpentine wire structures in which the spaces between the wires form the passages. Stents may be flat perforated structures that are subsequently rolled to form tubular structures or cylindrical structures that are woven, wrapped, drilled, etched or cut to form passages. Examples of stents that may be advantageously coated by the present process include but are not limited stents described in the following U.S. Patent Nos. 4,733,665 (hereinafter the Palmaz stent which is illustrated in Figure 1); 4,800,882 (hereinafter the Gianturco stent); 4,886,062 (hereinafter the Wiktor stent) and 5,514,154 (hereinafter the Guidant RX Multilink™ stent). These stents can be made of biocompatible materials including biostable and bioabsorbable materials. Suitable biocompatible metals include, but are not limited to, stainless steel, tantalum, titanium alloys (including nitinol), and cobalt alloys (including cobalt-chromium-nickel alloys). Suitable nonmetallic biocompatible materials include, but are not limited to, polyamides, polyolefins (i.e. polypropylene, polyethylene etc.), nonabsorbable polyesters (i.e. polyethylene terephthalate), and bioabsorbable aliphatic polyesters (i.e. homopolymers and copolymers of lactic acid, glycolic acid, lactide, glycolide, para-dioxanone, trimethylene carbonate, ε-caprolactone, etc. and blends thereof).

[0018] The present invention utilizes fluid flow or movement through the passages in the perforated medical device to avoid the formation of blockages or bridges. The fluid flow can be provided by active flow systems such as a perforated manifold inserted in the stent to circulate the coating fluid through the passages or can be created by placing the stent on a mandrel or in a small tube that is moved relative to the stent during the coating process to create sufficient fluid flow through the passages and thereby avoid the formation of blockages or bridges.

[0019] In one embodiment of the present invention as illustrated in Figure 2, a stent 2 is placed over a mandrel 6 that is smaller than the inner diameter d of the stent's intraluminal passage way 12 and dipped into the coating solution. The coated stent is moved relative to the mandrel after it is removed from the coating solution (preferably in one direction). Figure 3 illustrates the movement of the stent 2 relative to the mandrel 6 after it is removed from bath. The relative outer diameter of the mandrel and inner diameter of the stent are such that after dipping, while the coating is still wet, the movement of the stent along the mandrel's length clears the passages (slots) 10 which remain so on drying. The relative motion of the stent and mandrel, with limited clearance between the stent and mandrel, generates high shear rates which break the surface tension associated with the coating film filling the slots and provides smooth, defect free coating on the stent. Preferably the stent will be moved to an area of the mandrel that has not contacted the coating solution. As is illustrated in Figure 3 that provides a perspective view of the stent 2 after being coated with coating 14. There are additional advantages: the coatings can be of high concentration and by proper choice of the mandrel diameter to stent diameter (the clearance), the relative thickness of the inner and outer coating of the stent can be controlled. For example, the stent coating can be thicker on the outer surface to contact the luminal wall or thicker on the interior surface to interact with the fluid stream.

[0020] The mandrel may be of varying designs (i.e. tapered cones, cylindrical, slotted cylinders, mandrels having cross-sections that are ovoid, triangular or polygonal and would include shafts with veins or paddles). Additionally, the movement of the mandrel relative to the stent may not only be laterally, but may also consist of rotational movement. Object of the mandrel design being to assure sufficient shear flow relative to the passages to insure that the passages do not be come blocked.

[0021] Film-forming polymers that can be used for coatings in this application can be absorbable or non-absorbable and must be biocompatible to minimize irritation to the vessel wall. The polymer may be either biostable or bioabsorbable depending on the desired rate of release or the desired degree of polymer stability, but a bioabsorbable polymer

is preferred since, unlike biostable polymer, it will not be present long after implantation to cause any adverse, chronic local response. Furthermore, bioabsorbable polymers do not present the risk that over extended periods of time there could be an adhesion loss between the stent and coating caused by the stresses of the biological environment that could dislodge the coating and introduce further problems even after the stent is encapsulated in tissue.

[0022] Suitable film-forming bioabsorbable polymers that could be used include polymers selected from the group consisting of aliphatic polyesters, poly(amino acids), copoly(ether-esters), polyalkylenes oxalates, polyamides, poly (iminocarbonates), polyorthoesters, polyoxaesters, polyamidoesters, polyoxaesters containing amido groups, poly(anhydrides), polyphosphazenes, biomolecules and blends thereof. For the purpose of this invention aliphatic polyesters include homopolymers and copolymers of lactide (which includes lactic acid d-,l- and meso lactide), ε-caprolactone, glycolide (including glycolic acid), hydroxybutyrate, hydroxyvalerate, para-dioxanone, trimethylene carbonate (and its alkyl derivatives), 1,4-dioxepan-2-one, 1,5-dioxepan-2-one, 6,6-dimethyl-1,4-dioxan-2-one and polymer blends thereof. Poly(iminocarbonate) for the purpose of this invention include as described by Kemnitzer and Kohn, in the Handbook of Biodegradable Polymers, edited by Domb, Kost and Wisemen, Hardwood Academic Press, 1997, pages 251-272. Copoly(ether-esters) for the purpose of this invention include those copolyester-ethers described in Journal of Biomaterials Research, Vol. 22, pages 993-1009, 1988 by Cohn and Younes and Cohn, Polymer Preprints (ACS Division of Polymer Chemistry) Vol. 30(1), page 498, 1989 (e.g. PEO/PLA). Polyalkylene oxalates for the purpose of this invention include Patent Nos. 4,208,511; 4,141,087; 4,130,639; 4,140,678; 4,105,034; and 4,205,399 (incorporated by reference herein) . Polyphosphazenes, co-, ter- and higher order mixed monomer based polymers made from L-lactide, D,L-lactide, lactic acid, glycolide, glycolic acid, para-dioxanone, trimethylene carbonate and ε-caprolactone such as are described by Allcock in The Encyclopedia of Polymer Science, Vol. 13, pages 31-41, Wiley Intersciences, John Wiley & Sons, 1988 and by Vandorpe, Schacht, Dejardin and Lemmouchi in the Handbook of Biodegradable Polymers, edited by Domb, Kost and Wisemen, Hardwood Academic Press, 1997, pages 161-182 (which are hereby incorporated by reference herein). Polyanhydrides from diacids of the form HOOC-C_6H_4-O-$(CH_2)_m$-O-C_6H_4-COOH where m is an integer in the range of from 2 to 8 and copolymers thereof with aliphatic alpha-omega diacids of up to 12 carbons. Polyoxaesters polyoxaamides and polyoxaesters containing amines and/or amido groups are described in one or more of the following U.S. Patent Nos. 5,464,929; 5,595,751; 5,597,579; 5,607,687; 5,618,552; 5,620,698; 5,645,850; 5,648,088; 5,698,213 and 5,700,583; (which are incorporated herein by reference). Polyorthoesters such as those described by Heller in Handbook of Biodegradable Polymers, edited by Domb, Kost and Wisemen, Hardwood Academic Press, 1997, pages 99-118 (hereby incorporated herein by reference). Film-forming polymeric biomolecules for the purpose of this invention include naturally occurring materials that may be enzymatically degraded in the human body or are hydrolytically unstable in the human body such as fibrin, fibrinogen, collagen, elastin, and absorbable biocompatable polysaccharides such as chitosan, starch, fatty acids (and esters thereof), glucoso-glycans and hyaluronic acid.

[0023] Suitable film-forming biostable polymers with relatively low chronic tissue response, such as polyurethanes, silicones, poly(meth)acrylates, polyesters, polyalkyl oxides (polyethylene oxide), polyvinyl alcohols, polyethylene glycols and polyvinyl pyrrolidone, as well as, hydrogels such as those formed from crosslinked polyvinyl pyrrolidinone and polyesters could also be used. Other polymers could also be used if they can be dissolved, cured or polymerized on the stent. These include polyolefins, polyisobutylene and ethylene-alphaolefin copolymers; acrylic polymers (including methacrylate) and copolymers, vinyl halide polymers and copolymers, such as polyvinyl chloride; polyvinyl ethers, such as polyvinyl methyl ether; polyvinylidene halides such as polyvinylidene fluoride and polyvinylidene chloride; polyacrylonitrile, polyvinyl ketones; polyvinyl aromatics such as polystyrene; polyvinyl esters such as polyvinyl acetate; copolymers of vinyl monomers with each other and olefins, such as etheylene- methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins and ethylene-vinyl acetate copolymers; polyamides,such as Nylon 66 and polycaprolactam; alkyd resins; polycarbonates; polyoxymethylenes; polyimides; polyethers; epoxy resins, polyurethanes; rayon; rayon-triacetate, cellulose, cellulose acetate, cellulose acetate butyrate; cellophane; cellulose nitrate; cellulose propionate; cellulose ethers (i.e. carboxymethyl cellulose and hydoxyalkyl celluloses); and combinations thereof. Polyamides for the purpose of this application would also include polyamides of the form-NH-$(CH_2)_n$-CO- and NH-$(CH_2)_x$-NH-CO-$(CH_2)_y$-CO, wherein n is preferably an integer in from 6 to 13; x is an integer in the range of form 6 to 12; and y is an integer in the range of from 4 to 16. The list provided above is illustrative but not limiting.

[0024] The polymers used for coatings must be film-forming polymers that have molecular weight high enough as to not be waxy or tacky. The polymers also must adhere to the stent and not be so readily deformable after deposition on the stent as to be able to be displaced by hemodynamic stresses. The polymers molecular weight be high enough to provide sufficient toughness so that the polymers will not to be rubbed off during handling or deployment of the stent and must not crack during expansion of the stent. The melting point of the polymer used in the present invention should have a melting temperature above 40°C, preferably above about 45°C, more preferably above 50°C and most preferably above 55°C.

[0025] The preferable coatings to use for this application are bioabsorbable elastomers, more preferably aliphatic polyester elastomers. In the proper proportions aliphatic polyester copolymers are elastomers. Elastomers present the advantage that they tend to adhere well to the metal stents and can withstand significant deformation without cracking.

The high elongation and good adhesion provide superior performance to other polymer coatings when the coated stent is expanded. Examples of suitable bioabsorbable elastomers are described in U.S. Patent No. 5,468,253 hereby incorporated by reference. Preferably the bioabsorbable biocompatible elastomers based on aliphatic polyester, including but not limited to those selected from the group consisting of elastomeric copolymers of ε-caprolactone and glycolide (preferably having a mole ratio of ε-caprolactone to glycolide of from about 35:65 to about 65:35, more preferably 45:55 to 35:65) elastomeric copolymers of E-caprolactone and lactide, including L-lactide, D-lactide blends thereof or lactic acid copolymers (preferably having a mole ratio of ε-caprolactone to lactide of from about 35:65 to about 90:10 and more preferably from about 35:65 to about 65:35 and most preferably from about 45:55 to 30:70 or from about 90:10 to about 80:20) elastomeric copolymers of p-dioxanone (1,4-dioxan-2-one) and lactide including L-lactide, D-lactide and lactic acid (preferably having a mole ratio of p-dioxanone to lactide of from about 40:60 to about 60:40) elastomeric copolymers of ε-caprolactone and p-dioxanone (preferably having a mole ratio of ε-caprolactone to p-dioxanone of from about 30:70 to about 70:30) elastomeric copolymers of p-dioxanone and trimethylene carbonate (preferably having a mole ratio of p-dioxanone to trimethylene carbonate of from about 30:70 to about 70:30), elastomeric copolymers of trimethylene carbonate and glycolide (preferably having a mole ratio of trimethylene carbonate to glycolide of from about 30:70 to about 70:30), elastomeric copolymer of trimethylene carbonate and lactide including L-lactide, D-lactide, blends thereof or lactic acid copolymers (preferably having a mole ratio of trimethylene carbonate to lactide of from about 30:70 to about 70:30) and blends thereof. As is well known in the art these aliphatic polyester copolymers have different hydrolysis rates, therefore, the choice of elastomer may in part be based on the requirements for the coatings adsorption. For example ε-caprolactone-co-glycolide copolymer (45:55 mole percent, respectively) films lose 90% of their initial strength after 2 weeks in simulated physiological buffer whereas the ε-caprolactone-co-lactide copolymers (40:60 mole percent, respectively) loses all of its strength between 12 and 16 weeks in the same buffer. Mixtures of the fast hydrolyzing and slow hydrolyzing polymers can be used to adjust the time of strength retention.

[0026] The preferred bioabsorbable elastomeric polymers should have an inherent viscosity of from about 1.0 dL/g to about 4 dL/g, preferably an inherent viscosity of from about 1.0 dL/g to about 2 dL/g and most preferably an inherent viscosity of from about 1.2 dL/g to about 2 dL/g as determined at 25°C in a 0.1 gram per deciliter (g/dL) solution of polymer in hexafluoroisopropanol (HFIP).

[0027] The solvent is chosen such that there is the proper balance of viscosity, deposition level of the polymer, solubility of the pharmaceutical agent, wetting of the stent and evaporation rate of the solvent to properly coat the stents. In the preferred embodiment, the solvent is chosen such the pharmaceutical agent and the polymer are both soluble in the solvent. In some cases, the solvent must be chosen such that the coating polymer is soluble in the solvent and such that pharmaceutical agent is dispersed in the polymer solution in the solvent. In that case the solvent chosen must be able to suspend small particles of the pharmaceutical agent without causing them to aggregate or agglomerate into collections of particles that would clog the slots of the stent when applied. Although the goal is to dry the solvent completely from the coating during processing, it is a great advantage for the solvent to be non-toxic, non-carcinogenic and environmentally benign. Mixed solvent systems can also be used to control viscosity and evaporation rates. In all cases, the solvent must not react with or inactivate the pharmaceutical agent or react with the coating polymer. Preferred solvents include by are not limited to: acetone, N-methylpyrrolidone (NMP), dimethyl sulfoxide (DMSO), toluene, methylene chloride, chloroform, 1,1,2-trichloroethane (TCE), various freons, dioxane, ethyl acetate, tetrahydrofuran (THF), dimethylformamide (DMF), and dimethylacetamide (DMAC).

[0028] The film-forming biocompatible polymer coatings are generally applied to reduce local turbulence in blood flow through the stent, as well as, adverse tissue reactions. The coating may also be used to administer a pharmaceutically active material to the site of the stents placement. Generally, the amount of polymer coating to be placed on the stent will vary with the polymer and the stent design and the desired effect of the coating. As a guideline the amount of coating may range from about 0.5 to about 20 as a percent of the total weight of the stent after coating and preferably will range from about 1 to about 15 percent. The polymer coatings may be applied in one or more coating steps depending on the amount of polymer to be applied. Different polymers may also be used for different layers in the stent coating. In fact it is highly advantageous to use a dilute first coating solution as primer to promote adhesion of a subsequent coating layers that may contain pharmaceutically active materials.

[0029] Additionally, a top coating can be applied to delay release of the pharmaceutical agent, or they could be used as the matrix for the delivery of a different pharmaceutically active material. The amount of top coatings on the stent may vary, but will generally be less than about 2000 μg, preferably the amount of top coating will be in the range of about 10 μg to about 1700 μg and most preferably in the range of from about 300 μg to about 1600 μg. Layering of coating of fast and slow hydrolyzing copolymers can be used to stage release of the drug or to control release of different agents placed in different layers. Polymer blends may also be used to control the release rate of different agents or to provide desirable balance of coating (i.e. elasticity, toughness etc.) and drug delivery characteristics (release profile). Polymers with different solubilities in solvents can be used to build up different polymer layers that may be used to deliver different drugs or control the release profile of a drug. For example since ε-caprolactone-co-lactide elastomers are soluble in ethyl acetate and ε-caprolactone-co-glycolide elastomers are not soluble in ethyl acetate. A

first layer of ε-caprolactone-co-glycolide elastomer containing a drug can be over coated with ε-caprolactone-co-glycolide elastomer using a coating solution made with ethyl acetate as the solvent. Additionally, different monomer ratios within a copolymer, polymer structure or molecular weights may result in different solubilities. For example, 45/55 ε-caprolactone-co-glycolide at room temperature is soluble in acetone whereas a similar molecular weight copolymer of 35/65 ε-caprolactone-co-glycolide is substantially insoluble within a 4 weight percent solution. The second coating (or multiple additional coatings) can be used as a top coating to delay the drug deliver of the drug contained in the first layer. Alternatively, the second layer could contain a different drug to provide for sequential drug delivery. Multiple layers of different drugs could be provided by alternating layers of first one polymer then the other. As will be readily appreciated by those skilled in the art numerous layering approaches can be used to provide the desired drug delivery.

[0030] The coatings can be used to deliver therapeutic and pharmaceutic agents such as, but not limited to: antiproliferative/antimitotic agents including natural products such as vinca alkaloids (i.e. vinblastine, vincristine, and vinorelbine), paclitaxel, epidipodophyllotoxins (i.e. etoposide, teniposide), antibiotics (dactinomycin (actinomycin D) daunorubicin, doxorubicin and idarubicin), anthracyclines, mitoxantrone, bleomycins, plicamycin (mithramycin) and mitomycin, enzymes (L-asparaginase which systemically metabolizes L-asparagine and deprives cells which don't have the capacity to synthesize their own asparagine); antiproliferative/antimitotic alkylating agents such as nitrogen mustards (mechlorethamine, cyclophosphamide and analogs, melphalan, chlorambucil), ethylenimines and methylmelamines (hexamethylmelamine and thiotepa), alkyl sulfonates-busulfan, nirtosoureas (carmustine (BCNU) and analogs, streptozocin),trazenes - dacarbazinine (DTIC) ; antiproliferative/antimitotic antimetabolites such as folic acid analogs (methotrexate), pyrimidine analogs (fluorouracil, floxuridine, and cytarabine), purine analogs and related inhibitors (mercaptopurine, thioguanine, pentostatin and 2-chlorodeoxyadenosine{cladribine}) ; platinum coordination complexes (cisplatin, carboplatin), procarbazine, hydroxyurea, mitotane, aminoglutethimide; hormones (i.e.estrogen); Anticoaglants (heparin, synthetic heparin salts and other inhibitors of thrombin); fibrinolytic agents (such as tissue plasminogen activator, streptokinase and urokinase); antiplatelet:(aspirin, dipyridamole, ticlopidine, clopidogrel, abciximab); antimigratory; antisecretory (breveldin); antiinflammatory: such as adrenocortical steroids (cortisol, cortisone, fludrocortisone, prednisone, prednisolone, 6a-methylprednisolone, triamcinolone, betamethasone, and dexamethasone), non-steroidal agents (salicylic acid derivatives i.e. aspirin; para-aminophenol derivatives i.e. acetominophen; Indole and indene acetic acids (indomethacin, sulindac, and etodalac), heteroaryl acetic acids (tolmetin, diclofenac, and ketorolac), arylpropionic acids (ibuprofen and derivatives), anthranilic acids (mefenamic acid, and meclofenamic acid), enolic acids (piroxicam, tenoxicam, phenylbutazone, and oxyphenthatrazone), nabumetone, gold compounds (auranofin, aurothioglucose, gold sodium thiomalate); immunosuppressive: (cyclosporine, tacrolimus (FK-506), sirolimus (rapamycin), azathioprine, mycophenolate mofetil); Angiogenic: vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF); nitric oxide donors; anti-sense olgio nucleotides and combinations thereof.

[0031] Coating may be formulated by mixing one or more therapeutic agents with the coating polymers in a coating mixture. The therapeutic agent may be present as a liquid, a finely divided solid, or any other appropriate physical form. Optionally, the mixture may include one or more additives, e.g., nontoxic auxiliary substances such as diluents, carriers, excipients, stabilizers or the like. Other suitable additives may be formulated with the polymer and pharmaceutically active agent or compound. For example hydrophilic polymers selected from the previously described lists of biocompatible film forming polymers may be added to a biocompatible hydrophobic coating to modify the release profile (or a hydrophobic polymer may be added to a hydrophilic coating to modify the release profile). One example would be adding a hydrophilic polymer selected from the group consisting of polyethylene oxide, polyvinyl pyrrolidone, polyethylene glycol, carboxylmethyl cellulose, hydroxymethyl cellulose and combination thereof to an aliphatic polyester coating to modify the release profile. Appropriate relative amounts can be determined by monitoring the in vitro and/or in vivo release profiles for the therapeutic agents.

[0032] The best conditions for the coating application are when the polymer and pharmaceutic agent have a common solvent. This provides a wet coating that is a true solution. Less desirable, yet still usable are coatings that contain the pharmaceutic as a solid dispersion in a solution of the polymer in solvent. Under the dispersion conditions, care must be taken to ensure that the particle size of the dispersed pharmaceutical powder, both the primary powder size and its aggregates and agglomerates, is small enough not to cause an irregular coating surface or to clog the slots of the stent that we need to keep coating-free. In cases where a dispersion is applied to the stent and we want to improve the smoothness of the coating surface or ensure that all particles of the drug are fully encapsulated in the polymer, or in cases where we may want to slow the release rate of the drug, deposited either from dispersion or solution, we can apply a clear (polymer only) top coat of the same polymer used to provide sustained release of the drug or another polymer that further restricts the diffusion of the drug out of the coating. The top coat can be applied by dip coating with mandrel as previously described or by spray coating (loss of coating during spray application is less problematic for the clear topcoat since the costly drug is not included). Dip coating of the top coat can be problematic if the drug is more soluble in the coating solvent than the polymer and the clear coating redissolves previously deposited drug. The time spent in the dip bath may need to be limited so that the drug is not extracted out into the drug-free bath. Drying should be rapid so that the previously deposited drug does not completely diffuse into the topcoat.

[0033] The amount of therapeutic agent will be dependent upon the particular drug employed and medical condition being treated. Typically, the amount of drug represents about 0.001% to about 70%, more typically about 0.001% to about 60%, most typically about 0.001% to about 45% by weight of the coating.

[0034] The quantity and type of polymers employed in the coating layer containing the pharmaceutic agent will vary depending on the release profile desired and the amount of drug employed. The product may contain blends of the same or different polymers having different molecular weights to provide the desired release profile or consistency to a given formulation.

[0035] Absorbable polymers upon contact with body fluids including blood or the like, undergoes gradual degradation (mainly through hydrolysis) with concomitant release of the dispersed drug for a sustained or extended period (as compared to the release from an isotonic saline solution). Nonabsorbable and absorbable polymers may release dispersed drug by diffusion. This can result in prolonged delivery (over, say 1 to 2,000 hours, preferably 2 to 800 hours) of effective amounts (say, 0.001 $\mu g/cm^2$-min to 100 $\mu g/cm^2$-min) of the drug. The dosage can be tailored to the subject being treated, the severity of the affliction, the judgment of the prescribing physician, and the like.

[0036] Individual formulations of drugs and polymers may be tested in appropriate *in vitro* and *in vivo* models to achieve the desired drug release profiles. For example, a drug could be formulated with a polymer (or blend) coated on a stent and placed in an agitated or circulating fluid system (such as PBS 4% bovine albumin). Samples of the circulating fluid could be taken to determine the release profile (such as by HPLC). The release of a pharmaceutical compound from a stent coating into the interior wall of a lumen could be modeled in appropriate porcine system. The drug release profile could then be monitored by appropriate means such as, by taking samples at specific times and assaying the samples for drug concentration (using HPLC to detect drug concentration). Thrombus formation can be modeled in animal models using the ^{111} In-platelet imaging methods described by Hanson and Harker, Proc. Natl. Acad. Sci. USA 85:3184-3188 (1988). Following this or similar procedures, those skilled in the art will be able to formulate a variety of stent coating formulations.

Example 1

[0037] An absorbable elastomer based on 45:55 mole percent copolymer of ε-caprolactone and glycolide, with an IV of 1.58 (0.1 g/dl in hexafluoroisopropanol[HFIP] at 25°C) was dissolved five percent (5%) by weight in acetone and separately fifteen percent (15%) by weight in 1,1,2-trichloroethane. The synthesis of the elastomer is described in U. S. Patent 5,468,253 incorporated herein by reference. Gentle heating can be used to increase the dissolution rate. The high concentration coating could be formulated with or without pharmaceutical agent present. An initial primer coat of only the polymer is put on Cordis P-S 153 stent (commercially available from Cordis, a Johnson & Johnson Company) by dip coating in the five percent (5%) solution while the stent is placed on a 0.032 inch (0.81mm) diameter mandrel. The mandrel, with the stent on it, is removed from the dip bath and before the coating has a chance to dry the stent is moved along the length on the mandrel in one direction. This wiping motion applies high shear to the coating trapped between the stent and the mandrel. The high shear rate forces the coating out through the slots cut into the tube from which the stent is formed. This wiping action serves to force the coating out of the slots and keeps them clear. The "primed stent" is allowed to air dry at room temperature. The prime coat is about 100 micrograms of coating. After 1-2 hours of air drying, the stent is remounted on a 0.0355 inch (0.9mm) clean mandrel and dipped into a second, concentrated coat solution. This can be drug free or can contain about six percent (6%) by weight drug in addition to about fifteen percent (15%) polymer by weight in the coating solution. The dip and wipe process is repeated. The final coated stent is air dried for 12 hours and then put in a 60°C vacuum oven (at 30 in Hg vacuum) for 24 hours to dry. This method provides a coated stent with about 270 micrograms of polymer and about 180 micrograms of drug.

Example 2

[0038] This example describes experiments that demonstrate the ability of the dip and wipe coating approach to incorporate a bioactive agent in the coating and that the bioactive agent retains its biological activity. An initial primer coat of only the polymer described in Example 1 was placed on Cordis P-S 153 stent by dip coating in the five percent (5%) solution by weight while the stent is placed on a 0.032 inch (0.81mm) diameter mandrel. And primed as described in Example 1. The coated stent was then coated a second time with a coating solution of polymer and drug. The coated stent was dipped and wipe coated using the mandrel and a high concentration drug-polymer (15% polymer, 1:100 drug: polymer, and 2000 U/ml heparin-benzalkonium chloride [HBAC]; all in 70/30 acetone/DMSO) solution by the method described in Example 1. The HBAC coated stents had a total coating weight of about 350 micrograms. Coated stents were sent to North American Science Assocites Inc. (Northwood, Ohio USA) for a standard rabbit whole blood clotting time assay. The assay was performed by placing the stents on the surface of the Tryptic Soy Agar (TSA) plate along with a negative control sample (glass tubing) and a positive control (HBAC coated glass tubing). The 15 X 150 mm TSA plate was flooded with 35 ml of whole rabbit blood, obtained by arterial draw of a euthanized rabbit. The test

plate was incubated in ambient room temp. For 20-40 minutes. Following the incubation period, the samples were removed from the thrombus formed in the plate using forceps. The test and control sections were observed for evidence of adherence to the thrombus formation upon removal.

[0039] The heparinized stents were proven to be nonthrombogenic as compared with the non-heparinized controls.

Example 3

[0040] This example describes experiments that demonstrate the ability of the dip and wipe coating approach to provide coated stent with high coating loading and no bridging of the slots in the stent. A Cordis P-S 153 stent was taken and dip coated into a five percent (5%) solution of the elastomeric 45:55 mole percent of ε-caprolactone and glycolide copolymer (IV= 1.58) described in Example 1. The stent was removed and allow to air dry for 1-2 hours at room temperature. The coating added to the stent was about 100-150 micrograms. The slots in the stent were bridged with dry coating film (Figure 5). A second Cordis P-S 153 was dipped and wipe coated with the coating solution containing fifteen percent (15%) polymer as described in Example 1. The stent was found to have slots free of coating and to be loaded with 300 micrograms of coating. Similar experiments were performed with the Cordis Crown™ stent, the Guidant RX Multilink™ stent and the AVE GFX ™stent. The results were identical, dipping and wipping over a mandril allows high concentration coatings to provide high coating build on a variety of stents without the adverse effect of bridging the slots.

Example 4

[0041] This example demonstrates the differential solubility of elastomeric ε-caprolactone and glycolide copolymers and elastomeric ε-caprolactone and lactide copolymers in ethyl acetate. 0.2 g of ε-caprolactone and glycolide copolymer (45/55, IV=1.5, Tm ~62°C) were placed in a flat bottom glass vial along with 4 grams of ethyl acetate. These were heated to about 50°C on a hot plate with stirring bar over night. The result was partial solution with clear polymer on the walls and a cloudy solution at 50°C but the polymer precipitated out and coated the walls of the vial when the temperature came back to room temperature (~25°C), Similarly, 0.2 g of ε-caprolactone and lactide copolymer (40/60, IV=1.5, Tm ~ 132°C) were placed in a flat bottom glass vial with 4 g of ethyl acetate made in a manner similar to that described in Example 11. These were heated to about 50°C on a hot plate with stirring bar over night. The particles first swelled and then went into solution. On cooling to room temperature the solution remained clear and uniform.

Example 5

[0042] Multiple Dipping.

P-S stents were coated from a 5% w/w 45:55 ε-caprolactone and glycolide solution as described in the example 1. The initial coating resulted in ~ 100 micrograms of total solid on the stent. The stents were dried and then coated from a 15% w/w 45:55 ε-caprolactone and glycolide and 6% w/w drug solution. The second step resulted in ~ 170 micrograms of total solid and ~ 60 micrograms of drug on the stent. Stents were coated again from the same second solution and an increment of 30 micrograms (a total of 200 micrograms) of total solid and an increment of 20 micrograms of drug (a total of 80 micrograms) was observed. However when the dried stents were coated again with the same second solution total weight gain of the solid and the drug remain same.

Example 6

[0043] This Example describes applying a top coating to a coated stent with an ultrasonic spraying device.

[0044] A five percent by weight coating solution is made using 45:55 ε-caprolactone and glycolide described in Example 1 in a solvent solution of TCE :Acetone (1:1, w/w)

[0045] The ultrasonic spray unit is composed of a SonoTek (New York, U.S.A.) broadband ultrasonic generator (model 60-05108) attached to a nozzle (model 06-04010) an oscillated at 60KHz to generate a mean droplet size of 31 microns. The power at which the system was operated was is 5.8 mWatts. The flow rate was adjusted to about 0.3 ml/min. The ultrasonic spray system was placed in a plastic bag containment system to eliminate air currents and to slow evaporation. Stents would be positioned 1.5-5 cm distance from the nozzle and had a dwell time in the spray cloud of about 15-40 seconds.

[0046] The stent would then be dried in ambient conditions for 18-24 hours and subsequently vacuum dried at 60°C for 24 hours. Approximately, 100-150 micrograms of polymer was deposited per top coating run. A mandrel can be used to prevent coating the inside of the stent if desired.

Example 7

[0047] This Example describes the preparation of coated stents containing various levels of rapamycin for *in vitro* drug release testing.

[0048] 0.06 gms of Rapamycin was dissolved into 0.8 gms of 15% CAP/GLY solution in 1,1,2 TCE. The resulting coating solution contained 33.3% w/w drug on a dry, solid-only basis. Stents were coated by the method described in Example 1 and the coated stents were designated as `Std 33%'.

[0049] 0.015 gms of Rapamycin was dissolved into 0.5 gms of 18% CAP/GLY solution in 1,1,2 TCE. The resulting coating solution contained 14.3% w/w drug on a dry, solid-only basis. Stents were coated by the method described in Example 1 and the coated stents were designated as '14%'

[0050] 0.028 gms of rapamycin was dissolved into 0.5 gm of 18% CAP/GLY solution in 1,1,2 TCE. The resulting coating solution contained 23.7% w/w drug on a dry, solid-only basis. Stents were coated by the method described in Example 1. The dip-coated stents were spray coated with polymer-only solution as described in Example 6. The final coated stents were designated as '24-TC%'

[0051] 0.028 gms of rapamycin was dissolved into 0.5 gm of 18% CAP/GLY solution in 1,1,2 TCE. The resulting coating solution contained 23.7% w/w drug on a dry, solid-only basis. Stents were coated by the method described in Example 1. The dip-coated stents were spray coated with polymer-only solution as described in Example 6; However, a total volume of 200 microliters of spray solution was used in this case. The final coated stents were designated as '24- Thick TC%'

[0052] 0.06 gms of rapamycin was dissolved into 0.8 gm of 15% CAP/GLY solution in 1,1,2 TCE. The resulting coating solution contained 33.3% w/w drug on a dry, solid-only basis. Stents were coated by the method described in Example 1. The dip-coated stents were spray coated twice with ε-caprolactone-co-lactide (Cap/Lac) solution as described in Example 4. The final coated stents were designated as '33-TC%'.

[0053] 0.06 gms of rapamycin was dissolved into 0.8 gm of 15% CAP/LAC solution in 1,1,2 TCE. The resulting coating solution contained 33.3% w/w drug on a dry, solid-only basis. Stents were coated by the method described in example 1. The dip-coated stents were spray coated twice with polymer-only solution as described in Example 6 (except ε-caprolactone-co-lactide was used as the copolymer). The final coated stents were designated as '33-C/L TC%'.

Example 8

[0054] This example describes the results of testing the *in vitro* drug release of rapamycin from coated stent. Coated stents were prepared as described in Example 7 with varying concentrations of rapamycin were tested for the in vitro release of rapamycin into an aqueous ethanol solution. As is indicated in Figure 7, the stents denoted by the diamonds had a primer coating and a base coating that contained rapamycin. The total weight of the coating and rapamycin on the each stent was approximately 450 μg and contained 33 percent by weight of rapamycin. The coating was a copolymer of ε-caprolactone-co-glycolide (45:55 mole percent) applied by dip coating. The squares represent data points for stents having a primer coating and a base coating containing rapamycin. The total weight of the coating and drug was approximately 450 μg, which contained 14 percent by weight rapamycin. The coating material was also a copolymer of ε-caprolactone-co-glycolide (45:55 mole percent) applied by dip coating. The triangles represent data points for stents that had a primer coating and a base coating containing rapamycin. A primer coating and base coating (ε-caprolactone-co-glycolide 45:55 mole percent) were applied by dip coating the stent. A top coat of 200 μg (ε-caprolactone-co-glycolide 45:55 mole percent) was then applied using an ultrasonic spray device. The total weight of the coating and rapamycin was 650-700 μg, which contained 24 percent by weight rapamycin. The Xs represent data points for stents that had a primer coat and a base coating containing rapamycin. The primer coating and base coating (ε-caprolactone-co-glycolide 45:55 mole percent) were applied by dip coating the stent. A top coat of 100 μg (ε-caprolactone-co-glycolide 45:55 mole percent) was then applied using an ultrasonic spray device. The total weight of the coating and rapamycin was 550-600 μg, which contained 24 percent by weight rapamycin. The asterisk represents data points for stents that was coated with a primer, a base coat and two top coats. The primer coating and base coating (ε-caprolactone-co-glycolide 45:55 mole percent) were applied by dip coating the stents. A top coat of 100 μg (ε-caprolactone-co-glycolide; 45:55 mole percent) was then applied using an ultrasonic spray device. The total weight of the coating and rapamycin was approximately 550 μg, which contained 33 percent by weight rapamycin. The circles represent data points for stents that were dip coated with ε-caprolactone-co-lactide (40:60 mole percent). The stents were then top coated with an ultrasonic spray with approximately 100 μg of ε-caprolactone-co-lactide. The total coating weighed about 550 μg and contained 33 percent by weight rapamycin.

[0055] Each stent was placed in a 2.5mL of release medium (aqueous ethanol; 15 percent by volume at room temperature) contained in a 13 X 100 mm culture tube. The tube was shaken in a water bath (INNOVA™ 3100; New Brunswick Scientific) at 200 rpm while maintaining ambient conditions. After a given time interval (ranging froml5 minutes to one day) the tubes were removed from the shaker and the respective stents carefully transferred to a fresh 2.5

ml Aliquot of release medium. The new tube was placed on the shaker and agitation resumed. A sample was removed from the aliquot, which had previously contained the stent and placed in a HPLC vial for determination of the rapamycin content by HPLC.

[0056] The HPLC system used to analyze the samples was a Waters Alliance with a PDA 996. This system is equipped with a photodiode array detector. 20µL of each sample was withdrawn and analyzed on a C_{18}-reverse phase column (Waters Symmetry™ Column: 4.6mm X 100mm RP_{18} 3.5 µm with a matching guard column) using a mobile phase consisting of acetonitrile/methanol/water (38:34:28 v/v) delivered at a flow rate of 1.2 mL/min. The column was maintained at 60°C through the analysis. Under these analytical conditions rapamycin had a retention time of 4.75± 0.1 minutes. The concentration was determined from a standard curve of concentration versus response (area-under the curve) generated from rapamycin standards in the range of from 50ng/mL to 50µg/mL.

[0057] The results from testing the coated stents described above is shown in Figure 7.

Example 9

[0058] The goal of this study was to assess the rate of release of rapamycin from polymer-coated stents introduced in vivo into the coronary arteries of Yorkshire pigs. At various times after introduction of stents, the pigs were euthanized and the coronary arteries removed, the stents dissected free of the artery and analysed for rapamycin content using loading assay previously described. Through comparison with the amount of rapamycin contained on control, non-implanted stents, the *in vivo* rate of rapamycin release from the polymer coatings could be determined.

Experimental Procedure:

[0059] Male Yorkshire pigs weighing were used for these experiments. Animals were anesthetized with xylazine (2 mg/kg, IM), ketamine (17mg/kg, IM) and atropine (0.02 mg/kg IM). Pigs were then intubated using standard procedure, and placed on flow-by oxygen with 1-2.5% volatile isoflurane for maintenance anesthesia via the endotracheal tube. Peripheral intravenous access was achieved by insertion of a 20 gauge Angiocath into the marginal ear vein; a 20 gauge arterial catheter was also placed in the ear for continuous blood pressure and heart rate monitoring.

[0060] To minimize the chance for clot formation at the stent site, animals were started on oral aspirin 325 mg per day three days prior to the planned procedure. Upon confirmation of adequate depth of anesthesia, the right inguinal region was shaved and sterilized, and sterilely draped. Aseptic technique was used throughout the remainder of the procedure. A linear incision parallel to the femoral vessels was made and the subcutaneous tissues dissected to the level of the artery. After adequate exposure, the femoral artery was isolated proximally with umbilical tape and distally with a 3.0 silk tie for hemostasis. Using surgical scissors, an arteriotomy was made, and an 8 Fr sheath inserted in the artery. Heparin 4,000 units and bretylium 75 mg were then administered intravenously after sheath insertion. Electrocardiogram, respiratory pattern, and hemodynamics were continuously monitored.

[0061] A hockey stick guiding catheter was inserted via the femoral sheath, and advanced to the left coronary ostium, whereupon left coronary cineangiography was performed. A single frame anteroposterior radiogram was developed, and the luminal diameters of the left anterior descending and circumflex arteries measured, in order to size the balloon-stent assembly for a prespecified balloon-to-artery ratio of approximately 1.1 - 1.2:1. Using guide catheter support and fluoroscopic guidance, a 0.014" guidewire was advanced into the lumen of the left anterior descending artery. Intracoronary stenting was performed by advancing a stent mounted on a conventional angioplasty balloon into position in the mid-portion of the left anterior descending artery. The stent was deployed by inflating the mounting balloon to 8 atmospheres for 30 seconds. Upon confirmation of vessel patency, the balloon and guidewire were removed from the left anterior descending artery, and the identical procedure was performed in the left circumflex artery. Upon completion of stent delivery in the left circumflex artery, the balloon and guidewire were withdrawn.

[0062] The guiding catheter and femoral arterial sheath were then removed, the femoral artery tied proximally with 3-0 silk suture for hemostasis and the inguinal incision was closed. After discontinuation of anesthesia, were returned to colony housing. Daily aspirin 325 mg was continued until euthanasia.

[0063] At various times after stent implantation, euthanasia was performed by overdose of pentobarbital administered IV. The chest was opened via a mid-sternal incision and the heart removed. Both the LAD and LCX were carefully dissected free of surrounding tissue. The stent was then dissected free of the arterial tissue and placed in a vial. The arterial tissue was frozen and stored for later analysis by HPLC.

[0064] Figure 7 illustrates a typical *in vivo* release curve for a stent coating consisting of 33% rapamycin in polycaprolactone-co-glycolide.

Example 10

[0065] This Example describes the *in vivo* testing of coated stents in a porcine coronary artery model.

[0066] This preliminary study was conducted to assess the ability of rapamycin released from ε-caprolactone-co-glycolide copolymer-coated stents to inhibit intimal hyperplasia in vivo. Fourteen days after receiving rapamycin-loaded or control polymer coated stents, the male Yorkshire pigs were euthanized and the coronary arteries removed, the vessels prepared for histological evaluation and analysed for the amount of intimal growth. Through comparison control metal stents and stents containing polymer only, the in vivo ability of rapamycin to prevent neointimal growth could be determined.

[0067] Ethylene oxide-sterilized Palmaz-Schatz stents were implanted under sterile conditions in anesthetized farm pigs weighing 38 to 48 kg. Twenty-four hours prior to stent implantation, animals were given aspirin (325 mg, p.o., qd) and ticlopidine (250 mg, p.o., qd) to control chronic thrombosis; both aspirin and ticlopidine were continued daily until sacrifice. Anesthesia was induced with ketamine (20 mg/kg, i.m.), xylazine (2 mg/kg, i.m.) and sodium pentobarbital (10 mg/kg as needed) and maintained on 1-2% isofluorane in oxygen. An 8 Fr sheath was placed in an asceptically isolated left carotid artery and used subsequently to conduct either an 8 Fr JL 3.5 guide catheter for coronary angiography or to place a 0.014 inch guidewire for balloon delivery of stents to the appropriate coronary arteries. Heparin (150 unit/kg) was administered intraprocedurally to prevent acute thrombosis. Four experimental groups were employed; 1) metal stent control; 2) metal stent coated with 45/55 (w/w) ε-caprolactone glycolide copolymer (CAP/GLY); 3) 32 μg rapamycin/stent formulated in CAP/GLY; 4) 166 μg rapamycin/stent formulated in CAP/GLY. Stents were deployed in both the LAD and LCX coronary arteries. Angiography was performed prior to, during, and immediately after stenting to both size the vessel for choice of balloon diameter (3.0, 3.5 or 4.0 mm) and to obtain measurements for determination of the balloon/artery ratio. Stents were deployed by inflating the delivery balloon to 8-10 ATM for 30 sec. Angiography was also performed at 14 days post-implantation to obtain final vessel diameter. Treatment groups were randomized and individual stents were implanted by an investigator who was blinded as to the treatment. However, only one treatment was employed in any given pig. Fourteen days after implantation, animals were killed, the vessels were perfusion fixed for 10 minutes at 100 mmHg with 10% formalin and then stored in 10% buffered formalin.

[0068] For histological assessment, the stented vessel was embedded in glycol methacrylate. Four 3 - 5 μm thick cross-sections taken at equal intervals along the length of the stent were placed on glass slides and prepared with Miller's Elastin stain. Histomorphometric measurements were determined in each section *via* microscopy and computerized image analysis. Individual values obtained for each vessel represent the average of the 4 measured sections. Differences between treatments were assessed by ANOVA and Dunnett's test.

Table 1.

	Histology		***Angiography***	
Treatment	***Intima/Med ia ratio***	***Intimal Area (mm^2)***	***% Diameter Stenosis***	***B/A Ratio***
Metal Control (n=10)	0.90 ± 0.05	3.65 ± 0.82	24.8 ±3.9[1]	1.27 ± 0.05
CAP/GLY (n=8)	0.91 ± 0.11	4.15 ± 0.23	38.0 ± 4.0	1.32 ± 0.04
CAP/GLY ± 32 μg rapamycin (n=10)	0.75 ± 0.04	3.27 ± + 0.16	21.6 ± 3.6[1]	1.23 ± 0.03
CAP/GLY ± 166 μg rapamycin (n=8)	0.65 ± 0.04[1,2]	2.87 ± 0.31	23.9 ± 2.3[1]	1.27 ± 0.05

[1] $p<0.05$ from CAP/GLY
[2] $p<0.05$ from Metal Control

All values are mean±sem. B/A ratio = balloon to artery ratio, an index of the consistency of stent expansion from group to group

[0069] As can be seen in Table 1, local delivery of rapamycin to injured coronary arteries resulted in a significant ($p<0.05$) reduction in intima:media ratio in the 166 μg treatment group and a small but non-significant reduction in the 32 μg treatment group when compared with the polymer and bare metal control groups. Rapamycin delivered from the GAP/GLY coating also resulted in non-significant dose-related decreases in neointimal area in both the 32 μg and 166 μg treatment groups. The percent diameter stenosis as assessed by angiography was also significantly reduced in the 2 rapamycin treatment groups when compared to the CAP/GLY group, although the reduction in this parameter from the metal control was small and non-significant. Never-the-less, in this preliminary 14 day study, these data suggest that local release of rapamycin from a biodegradable hydrophobic polymer coating may be capable of limiting the amount of neointimal proliferation which occurs as a result of stent deployment.

Example 11

[0070] In the glove box, 100 µL (33 µmol) of a 0.33 M stannous octoate solution in toluene, 115 µL (1.2 mmol) of diethylene glycol, 24.6 grams (170 mmol) of L-lactide, and 45.7 grams (400 mmol) of ε-caprolactone were transferred into a silanized, flame dried, two neck, 250 mL round bottom flask equipped with a stainless steel mechanical stirrer and a nitrogen gas blanket. The reaction flask was placed in an oil bath already set at 190°C and held there. Meanwhile, in the glove box, 62.0 grams (430 mmol) L-lactide were transferred into a flame dried, pressure equalizing addition funnel. The funnel was wrapped with heat tape and attached to the second neck of the reaction flask. After 6 hours at 190°C, the molten L-lactide was added to the reaction flask over 5 minutes. The reaction was continued overnight for a total reaction time of 24 hours at 190°C. The reaction was allowed to cool to room temperature overnight. The copolymer was isolated from the reaction flask by freezing in liquid nitrogen and breaking the glass. Any remaining glass fragments were removed from the copolymer using a bench grinder. The copolymer was again frozen with liquid nitrogen and broken off the mechanical stirring paddle. The copolymer was ground into a tared glass jar using a Wiley Mill and allowed to warm to room temperature in a vacuum oven overnight. 103.13 grams of 40:60 poly(ε-caprolactone-co-L-lactide) were added to a tared aluminum pan and then devolitilized under vacuum at 110°C for 54 hours. 98.7 grams (95.7% by weight) of copolymer were recovered after devolitilization.

Claims

1. A method for coating a stent having an outer surface and inner surface with passages between the outer and inner surfaces comprising:

   (a) contacting the stent with a liquid coating solution containing a film forming biocompatible polymer under conditions suitable to allow the film forming biocompatible polymer to coat at least one surface of the stent;
   (b) before the coating solution dries creating fluid movement out of the passages of the stent sufficient to prevent the film forming biocompatible polymer from substantially blocking said passages thereafter;
   (c) drying the stent to provide at least a partially coated stent with a first coating.

2. The method of claim 1 wherein the stent is contacted with the coating solution by dipping the stent into the coating solution or by spraying the coating solution on to the stent.

3. The method of claim 1 or claim 2 wherein fluid movement is created: by contacting a mandrel with the inner surface of the stent and moving the mandrel relative to the stent to prevent bridges from forming in said passages; or by contacting the outer surface of the stent with the inner surface of a tube and moving the tube relative to the stent to prevent bridges from forming in said passages.

4. The method of any of claims 1 to 3 wherein the film forming biocompatible polymer is an aliphatic polyester, a poly (amino acid), a copoly(ether-ester), a polyalkylene oxalate, a polyamide, a poly(iminocarbonate), a polyorthoester, a polyoxaester, a polyamidoester, a polyoxaester containing amido groups, a poly(anhydride), a polyphosphazene, a biomolecule or a blend thereof.

5. The method of claim 4 wherein the film forming polymer is a biocompatible aliphatic polyester, which is preferably elastomeric.

6. The method of claim 5 wherein the biocompatible aliphatic polyester is an elastomeric copolymer of ε-caprolactone and glycolide, an elastomeric copolymer of ε-caprolactone and lactide, an elastomeric copolymer of p-dioxanone and lactide, an elastomeric copolymer of ε-caprolactone and p-dioxanone, an elastomeric copolymer of p-dioxanone and trimethylene carbonate, an elastomeric copolymer of trimethylene carbonate and glycolide, an elastomeric copolymer of trimethylene carbonate and lactide or blend thereof.

7. The method of any one of claims 1 to 6 wherein additionally contained in the coating solution is a pharmaceutically active compound.

8. The method of claim 7 wherein the pharmaceutically active compound is: an antiproliferative/antimitotic agent; an antibiotic; an enzyme; an antiproliferative/antimitotic alkylating agent; an antiproliferative/antimitotic antimetabolite; a hormone; an anticoaglant; a fibrinolytic agent; an antiplatelet agent; an antimigratory agent; an antisecretory agent; an antiinflammatory agent; an immunosuppressive agent; an angiogenic agent; a nitric oxide donor; an anti-

sense oligonucleotide or a combination thereof, and is preferably rapamycin.

9. The method of any one of claims 1 to 8, wherein additionally present is a biocompatble hydrophilic polymer.

10. The method of any one of claims 1 to 9 wherein after the stent is dried a second coating is applied.

FIG. 1

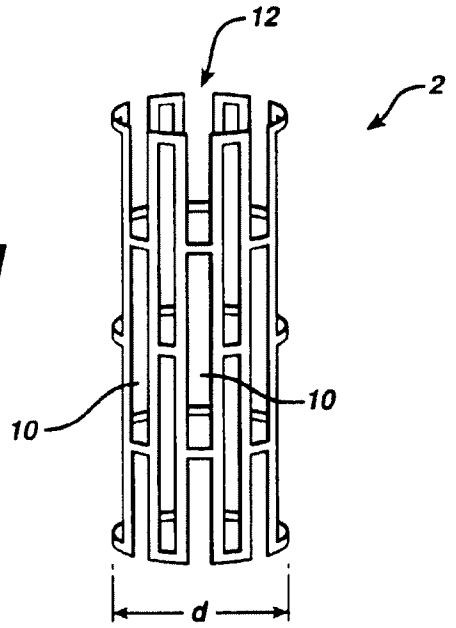

FIG. 2

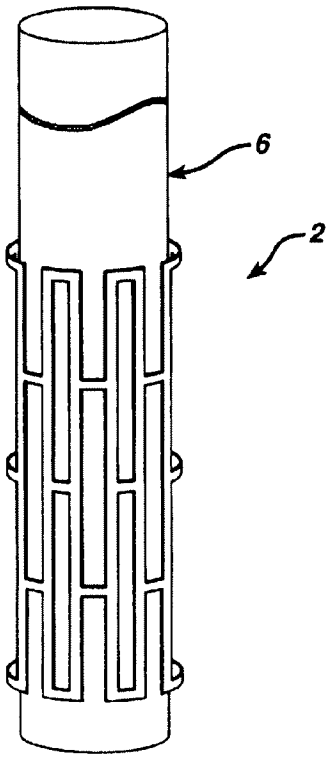

FIG. 3

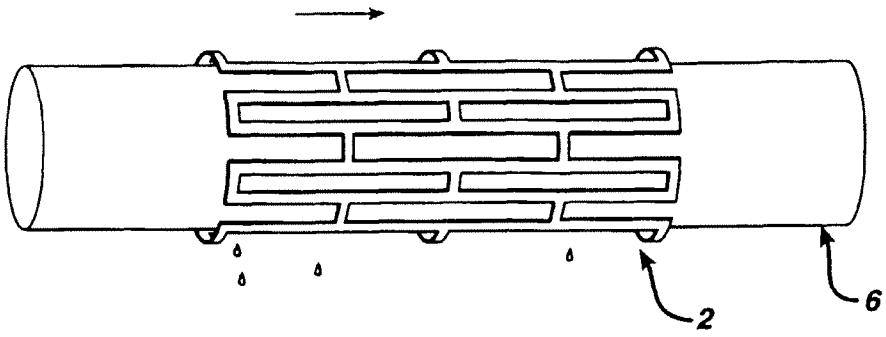

FIG. 4

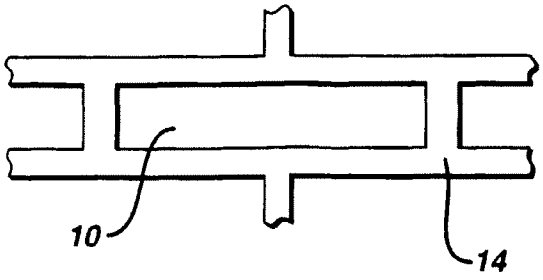

FIG. 5

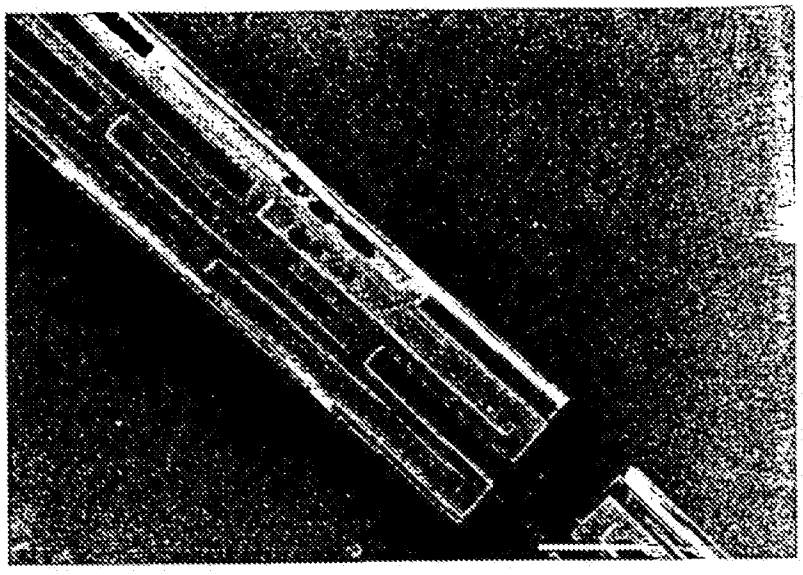

FIG. 6

FIG. 7

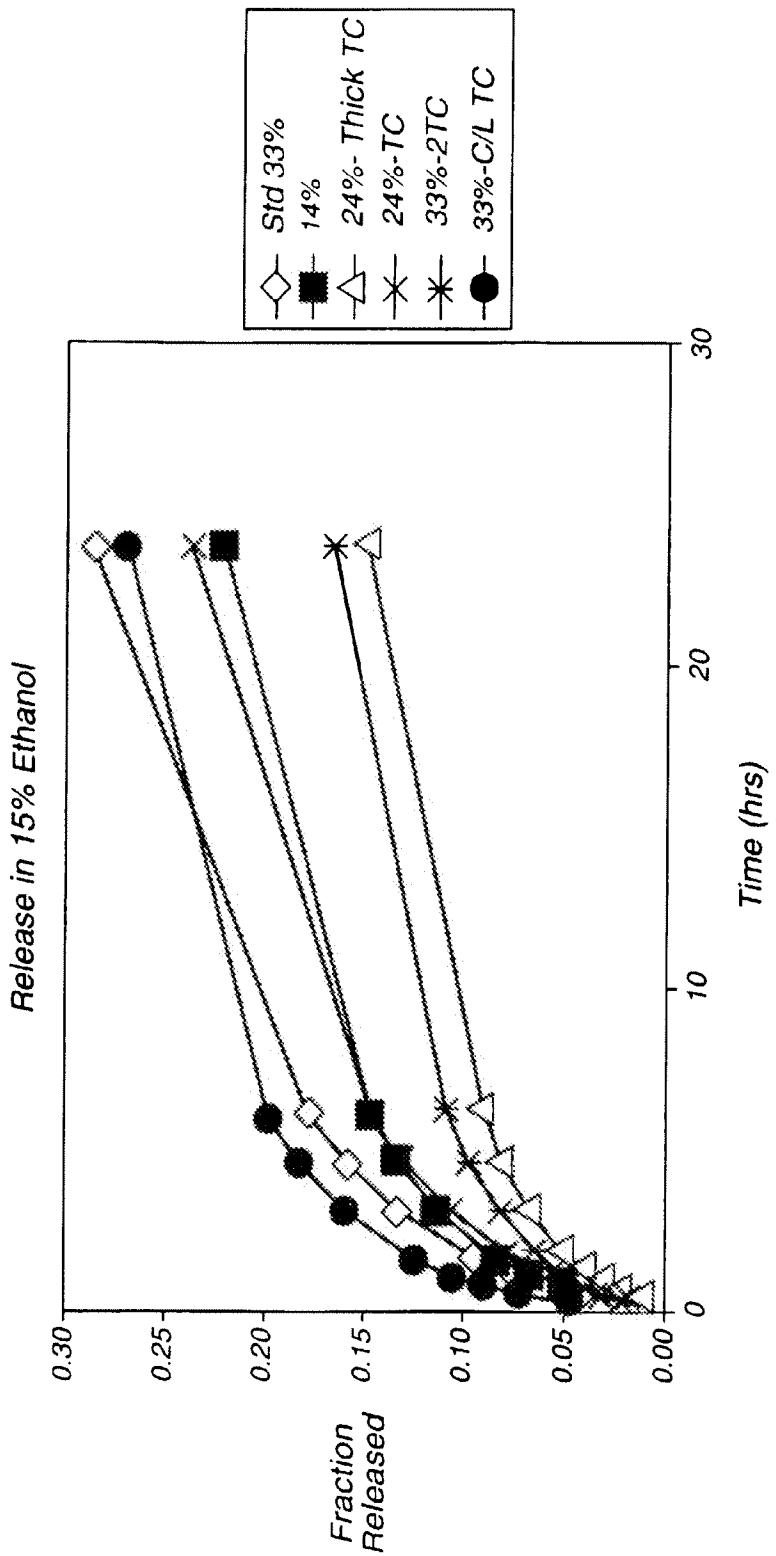
Release in 15% Ethanol
Fraction Released
0.30
0.25
0.20
0.15
0.10
0.05
0.00
0
10
20
30
Time (hrs)
Std 33%
14%
24%- Thick TC
24%-TC
33%-2TC
33%-C/L TC

FIG. 8

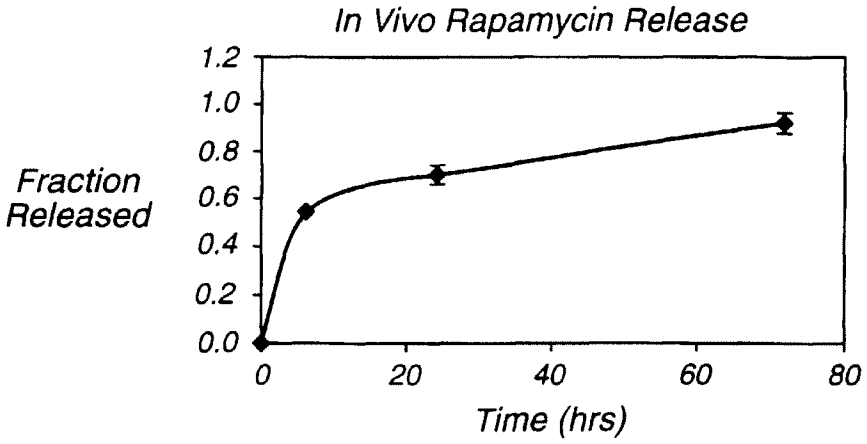
In Vivo Rapamycin Release
Fraction Released
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
Time (hrs)

EXHIBIT C

US 20040181271A1

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DeSimone et al. (43) Pub. Date: Sep. 16, 2004

(54) INTRALUMINAL PROSTHESES HAVING POLYMERIC MATERIAL WITH SELECTIVELY MODIFIED CRYSTALLINITY AND METHODS OF MAKING SAME

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Publication Classification

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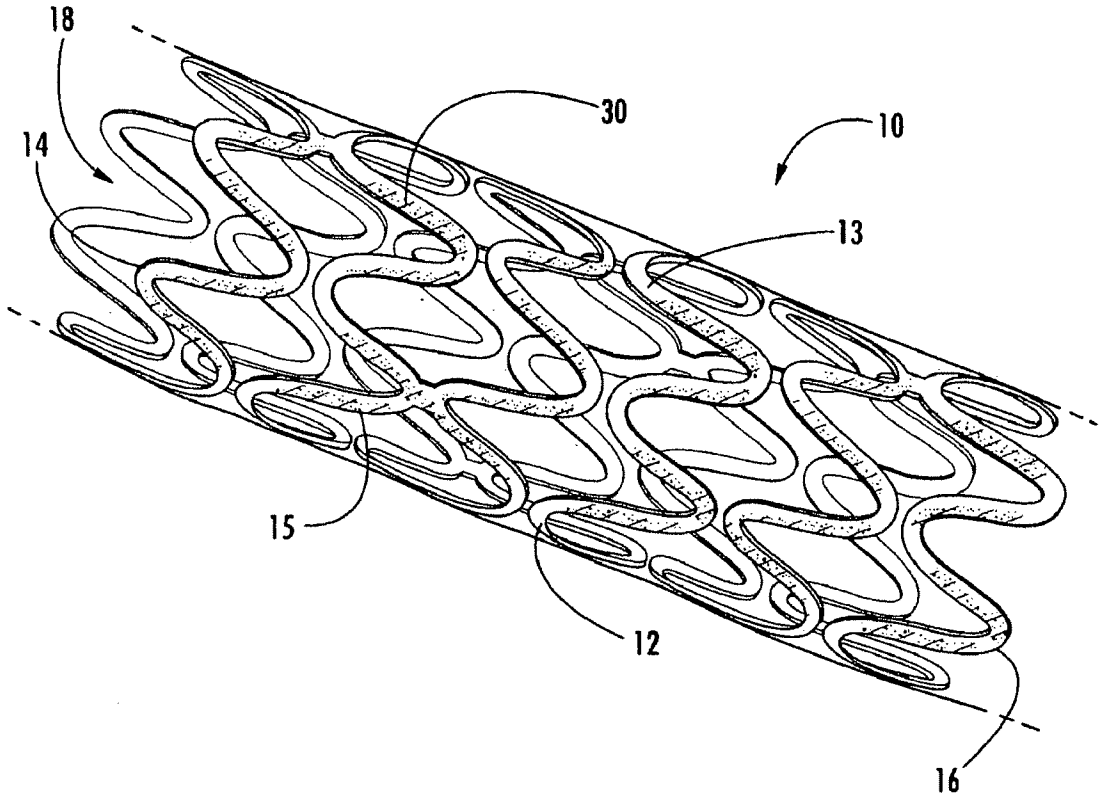
(52) **U.S. Cl.** **623/1.1**; 428/36.9

(57) **ABSTRACT**

Methods of manufacturing polymeric intraluminal prostheses include annealing the polymeric material to selectively modify the crystallinity thereof. Annealing may be utilized to selectively modify various properties of the polymeric material of an intraluminal prosthesis, including: selectively increasing the modulus of the polymeric material; selectively increasing the hoop strength of the intraluminal prosthesis; selectively modifying the elution rate (increase or decrease) of a pharmacological agent subsequently disposed on or within the annealed polymeric material; selectively increasing/decreasing stress in the intraluminal prosthesis; and selectively modifying the polymeric material such that it erodes at a different rate.



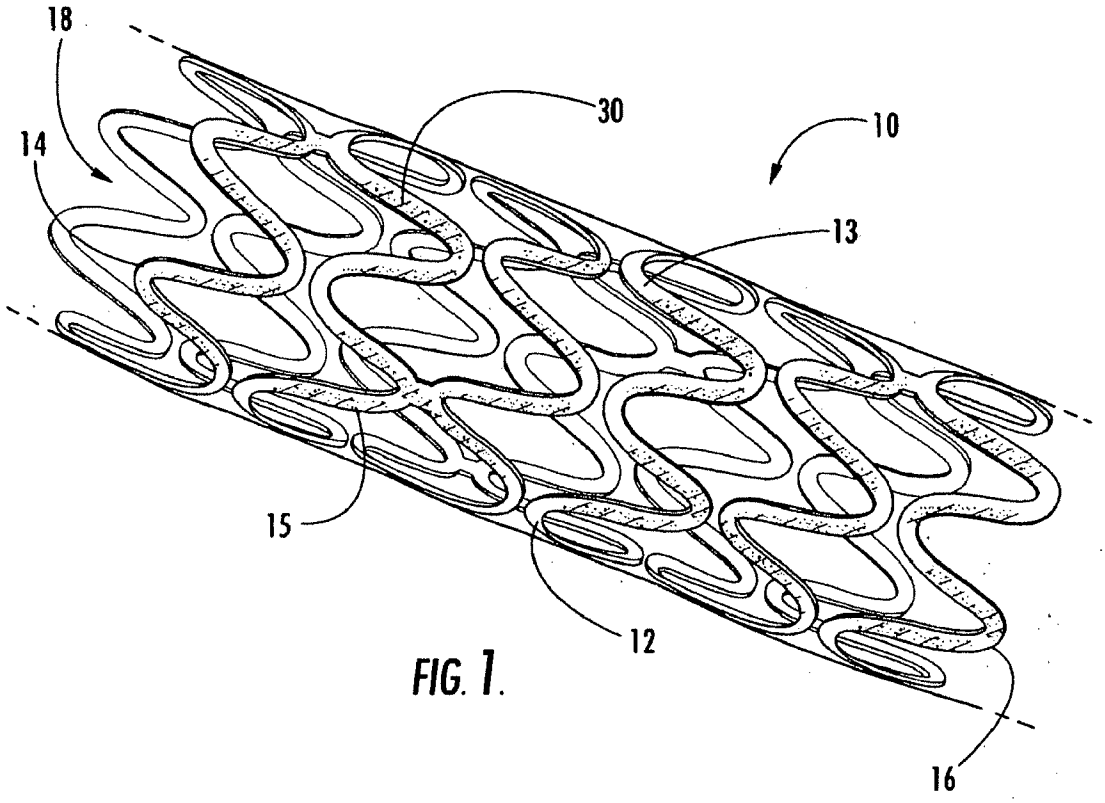


FIG. 1.

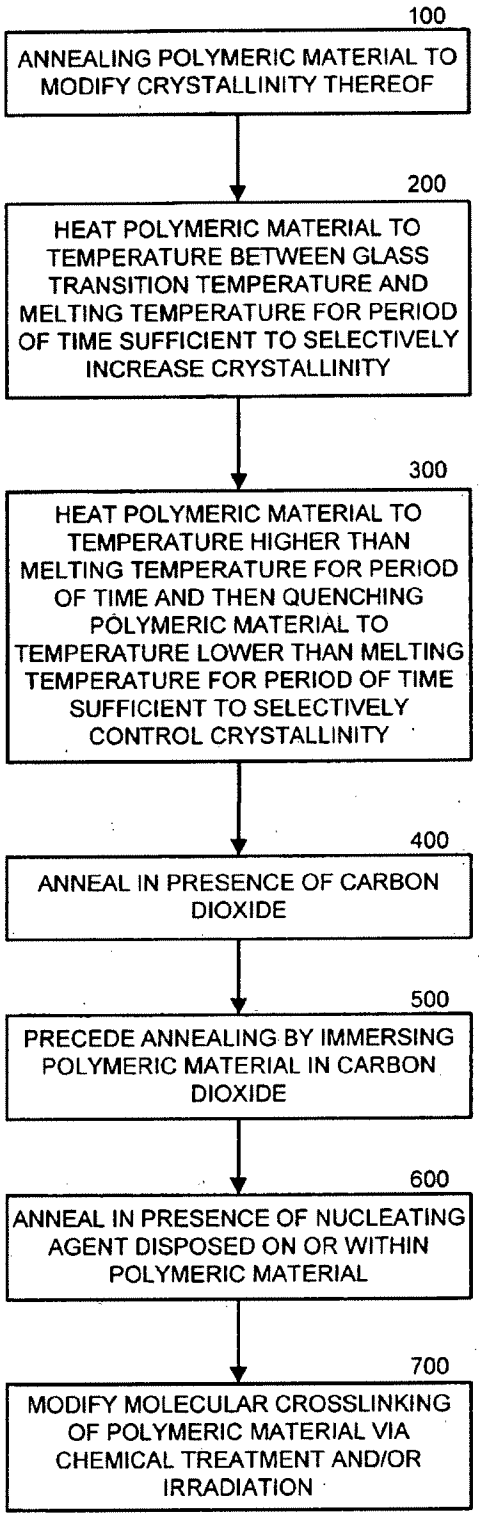

100
ANNEALING POLYMERIC MATERIAL TO MODIFY CRYSTALLINITY THEREOF
200
HEAT POLYMERIC MATERIAL TO TEMPERATURE BETWEEN GLASS TRANSITION TEMPERATURE AND MELTING TEMPERATURE FOR PERIOD OF TIME SUFFICIENT TO SELECTIVELY INCREASE CRYSTALLINITY
300
HEAT POLYMERIC MATERIAL TO TEMPERATURE HIGHER THAN MELTING TEMPERATURE FOR PERIOD OF TIME AND THEN QUENCHING POLYMERIC MATERIAL TO TEMPERATURE LOWER THAN MELTING TEMPERATURE FOR PERIOD OF TIME SUFFICIENT TO SELECTIVELY CONTROL CRYSTALLINITY
400
ANNEAL IN PRESENCE OF CARBON DIOXIDE
500
PRECEDE ANNEALING BY IMMERSING POLYMERIC MATERIAL IN CARBON DIOXIDE
600
ANNEAL IN PRESENCE OF NUCLEATING AGENT DISPOSED ON OR WITHIN POLYMERIC MATERIAL
700
MODIFY MOLECULAR CROSSLINKING OF POLYMERIC MATERIAL VIA CHEMICAL TREATMENT AND/OR IRRADIATION

Fig. 2

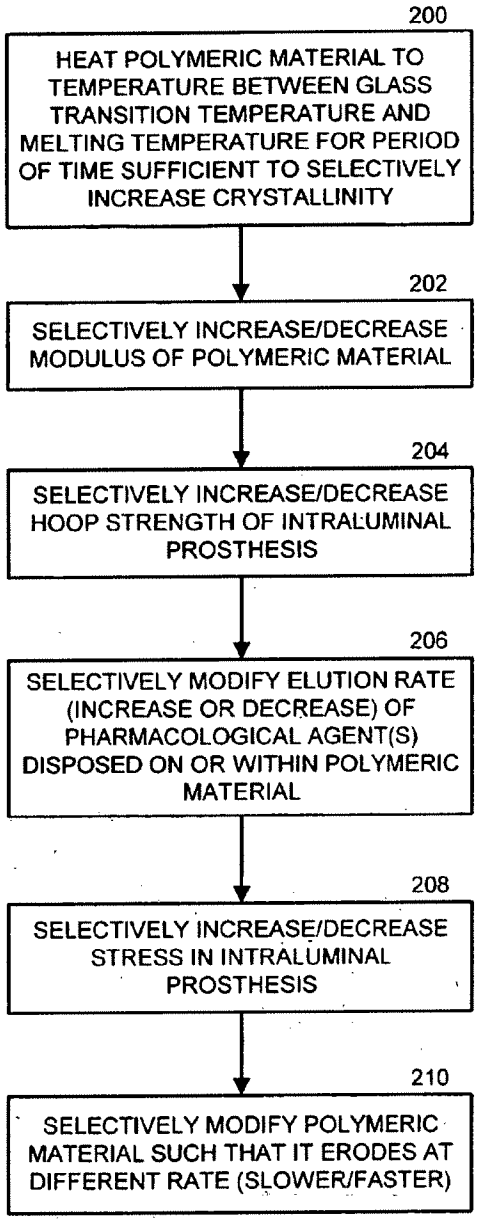

200
HEAT POLYMERIC MATERIAL TO TEMPERATURE BETWEEN GLASS TRANSITION TEMPERATURE AND MELTING TEMPERATURE FOR PERIOD OF TIME SUFFICIENT TO SELECTIVELY INCREASE CRYSTALLINITY
202
SELECTIVELY INCREASE/DECREASE MODULUS OF POLYMERIC MATERIAL
204
SELECTIVELY INCREASE/DECREASE HOOP STRENGTH OF INTRALUMINAL PROSTHESIS
206
SELECTIVELY MODIFY ELUTION RATE (INCREASE OR DECREASE) OF PHARMACOLOGICAL AGENT(S) DISPOSED ON OR WITHIN POLYMERIC MATERIAL
208
SELECTIVELY INCREASE/DECREASE STRESS IN INTRALUMINAL PROSTHESIS
210
SELECTIVELY MODIFY POLYMERIC MATERIAL SUCH THAT IT ERODES AT DIFFERENT RATE (SLOWER/FASTER)

Fig. 3

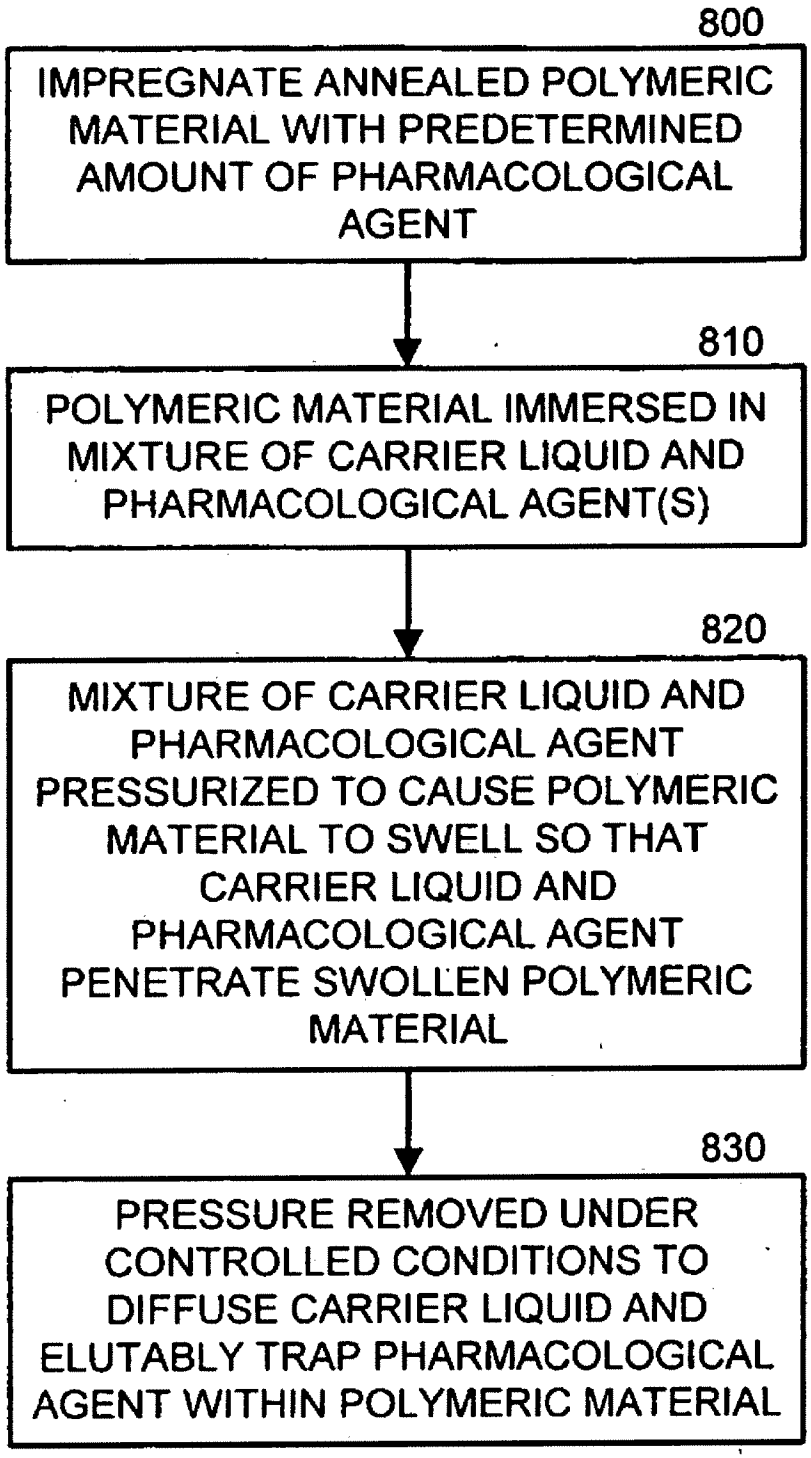

800
IMPREGNATE ANNEALED POLYMERIC MATERIAL WITH PREDETERMINED AMOUNT OF PHARMACOLOGICAL AGENT
810
POLYMERIC MATERIAL IMMERSED IN MIXTURE OF CARRIER LIQUID AND PHARMACOLOGICAL AGENT(S)
820
MIXTURE OF CARRIER LIQUID AND PHARMACOLOGICAL AGENT PRESSURIZED TO CAUSE POLYMERIC MATERIAL TO SWELL SO THAT CARRIER LIQUID AND PHARMACOLOGICAL AGENT PENETRATE SWOLLEN POLYMERIC MATERIAL
830
PRESSURE REMOVED UNDER CONTROLLED CONDITIONS TO DIFFUSE CARRIER LIQUID AND ELUTABLY TRAP PHARMACOLOGICAL AGENT WITHIN POLYMERIC MATERIAL

Fig. 4

INTRALUMINAL PROSTHESES HAVING POLYMERIC MATERIAL WITH SELECTIVELY MODIFIED CRYSTALLINITY AND METHODS OF MAKING SAME

RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 60/453,317, filed Mar. 10, 2003, the disclosure of which is incorporated herein by reference in its entirety as if set forth fully herein.

FIELD OF THE INVENTION

[0002] The present invention relates generally to medical devices and, more particularly, to intraluminal prostheses.

BACKGROUND OF THE INVENTION

[0003] Stents are typically used as adjuncts to percutaneous transluminal balloon angioplasty procedures, in the treatment of occluded or partially occluded arteries and other blood vessels. As an example of a balloon angioplasty procedure, a guiding catheter or sheath is percutaneously introduced into the cardiovascular system of a patient through a femoral artery and advanced through the vasculature until the distal end of the guiding catheter is positioned at a point proximal to the lesion site. A guidewire and a dilatation catheter having a balloon on the distal end are introduced through the guiding catheter with the guidewire sliding within the dilatation catheter. The guidewire is first advanced out of the guiding catheter into the patient's vasculature and is directed across the vascular lesion. The dilatation catheter is subsequently advanced over the previously advanced guidewire until the dilatation balloon is properly positioned across the vascular lesion. Once in position across the lesion, the expandable balloon is inflated to a predetermined size with a radiopaque liquid at relatively high pressure to radially compress the atherosclerotic plaque of the lesion against the inside of the artery wall and thereby dilate the lumen of the artery. The balloon is then deflated to a small profile so that the dilatation catheter can be withdrawn from the patient's vasculature and blood flow resumed through the dilated artery. Balloon angioplasty sometimes results in short or long term failure. That is, vessels may abruptly close shortly after the procedure or restenosis may occur gradually over a period of months thereafter. To counter restenosis following angioplasty, implantable intraluminal prostheses, commonly referred to as stents, are used to achieve long term vessel patency. A stent functions as scaffolding to structurally support the vessel wall and thereby maintain luminal patency, and are transported to a lesion site by means of a delivery catheter.

[0004] Types of stents may include balloon expandable stents, spring-like, self-expandable stents, and thermally expandable stents. Balloon expandable stents are delivered by a dilitation catheter and are plastically deformed by an expandable member, such as an inflation balloon, from a small initial diameter to a larger expanded diameter. Self-expanding stents are formed as spring elements which are radially compressible about a delivery catheter. A compressed self-expanding stent is typically held in the compressed state by a delivery sheath. Upon delivery to a lesion site, the delivery sheath is retracted allowing the stent to expand. Thermally expandable stents are formed from shape memory alloys which have the ability to expand from a small initial diameter to a second larger diameter upon the application of heat to the alloy.

[0005] It may be desirable to provide localized pharmacological treatment of a vessel at the site being supported by a stent. Thus, sometimes it is desirable to utilize a stent both as a support for a lumen wall as well as a delivery vehicle for one or more pharmacological agents. Unfortunately, the bare metallic materials typically employed in conventional stents are not generally capable of carrying and releasing pharmacological agents. Previously devised solutions to this dilemma have been to join drug-carrying polymers to metallic stents. Additionally, methods have been disclosed wherein the metallic structure of a stent has been formed or treated so as to create a porous surface that enhances the ability to retain applied pharmacological agents. However, these methods have generally failed to provide a quick, easy and inexpensive way of loading drugs onto intraluminal prostheses, such as stents. In addition, only small amounts of drugs can be loaded into thin polymeric coatings.

[0006] Intraluminal prostheses, such as stents have been developed using various polymeric materials and/or coatings of polymeric materials to overcome the limitations of conventional metallic prostheses. However, it would be desirable to be able to adjust various mechanical properties (e.g., modulus, hoop strength, flexibility, etc.) of polymeric intraluminal prostheses. For example, for intraluminal prostheses used to deliver pharmacological agents, it would be desirable to be able to adjust the elution rate of a pharmacological agent therefrom. As another example, it would be desirable to be able to adjust the degradation rate and/or the nature of degradation of the polymeric material.

SUMMARY OF THE INVENTION

[0007] According to embodiments of the present invention, methods of manufacturing polymeric intraluminal prostheses (e.g., formed from polymeric material or having a coating of polymeric material) include annealing the polymeric material to selectively modify the crystallinity or crystalline structure thereof. Annealing may include heating the polymeric material to a temperature between the glass transition temperature and the melting temperature (i.e., $T_g<T_{anneal}<T_m$) of the polymeric material for a period of time sufficient to selectively increase the crystallinity of the polymeric material.

[0008] Annealing may include initially heating the polymeric material to a temperature that is higher than the melting temperature (i.e., $T_{anneal}>T_m$) of the polymeric material for a period of time and then quenching the polymeric material to a temperature that is lower than the melting temperature (i.e., $T_{quench}<T_m$) for a period of time sufficient to selectively control or limit the crystallinity of the polymeric material. According to embodiments of the present invention, the quench temperature may be between the glass transition temperature and the melting temperature of the polymeric material (i.e., $T_g<T_{quench}<T_m$). According to embodiments of the present invention, the quench temperature may be lower than the glass transition temperature of the polymeric material (i.e., $T_{quench}<T_g$)

[0009] According to embodiments of the present invention, annealing may be utilized to selectively modify various properties of the polymeric material of an intraluminal

prosthesis. For example, annealing may include heating the polymeric material to a temperature between the glass transition temperature and the melting temperature (i.e., $T_g<T_{anneal}<T_m$) of the polymeric material for a period of time sufficient to: selectively increase the modulus of the polymeric material; selectively influence axial flexibility; selectively increase the hoop strength of the intraluminal prosthesis; selectively modify the elution rate (increase or decrease) of a pharmacological agent subsequently disposed on or within the annealed polymeric material; selectively decrease stress in the intraluminal prosthesis during expansion from the contracted configuration; and selectively modify the polymeric material such that it erodes at a different rate (i.e., slower or faster).

[0010] Annealing may be performed so as to selectively increase (or vary) crystallinity of one or more isolated portions of the polymeric material of an intraluminal prosthesis. This will allow for customization of intraluminal prostheses and allow for matching to anatomical and physiological environments. For example, crystallinity can be increased in a mid section of an intraluminal prosthesis to enhance mechanical strength and scaffolding capability thereof, while leaving the ends of the device more compliant so as to match the physical compliance of a non-diseased vessel wall.

[0011] According to embodiments of the present invention, crystallinity can be increased from about 30% to about 70% or greater in polymeric materials. Crystallinity plays an important role in determining both permeability and biodegradability because of the generally accepted fact that the bulk crystalline phase is inaccessible to water and other permeants. Thus, an increase in crystallinity reduces the permeability by both reducing solubility and increasing the tortuosity of the diffusional pathway.

[0012] Increasing crystallinity and orienting (uniaxially or biaxially) crystallites can improve mechanical properties including radial compressive strength and flexibility.

[0013] According to embodiments of the present invention, annealing may be performed in the presence of carbon dioxide (i.e., with the intraluminal prosthesis being annealed in contact with a carbon dioxide fluid). According to other embodiments of the present invention, annealing may be preceded by immersing the polymeric material in carbon dioxide.

[0014] According to embodiments of the present invention, annealing may be performed in the presence of a nucleating agent disposed on or within the polymeric material. Pharmacological agents disposed on or within the polymeric material may include, but are not limited to, agents selected from the following categories: antineoplastics, antimitotics, antiinflammatories, antiplatelets, anticoagulants, antifibrins, antithrombins, antiproliferatives, antibiotics, antioxidants, immunosuppressives, antiallergic substances, and combinations thereof.

[0015] According to other embodiments of the present invention, molecular crosslinking of the polymeric material of an intraluminal prostheses may be modified by subjecting the polymeric material to chemical treatment and/or irradiation. The polymeric material may be subjected to chemical treatment and/or irradiation before, during and/or after annealing. Such treatments may also act as a sterilization step.

[0016] According to other embodiments of the present invention, the annealed polymeric material of a prosthesis is impregnated with a predetermined amount of one or more pharmacological agents. According to embodiments of the present invention, a polymeric intraluminal prosthesis is immersed in a mixture of carrier fluid and pharmacological agent(s) such that one or more pharmacological agents are infused within the polymeric material or within a polymeric coating thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] **FIG. 1** is a perspective view of an intraluminal prosthesis produced in accordance with embodiments of the present invention.

[0018] **FIGS. 2-4** are flowcharts of operations for manufacturing polymeric intraluminal prostheses, according to embodiments of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[0019] The present invention now is described more fully hereinafter with reference to the accompanying drawings, in which embodiments of the invention are shown. This invention may, however, be embodied in many different forms and should not be construed as limited to the embodiments set forth herein; rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art.

[0020] The term "eluting" is used herein to mean the release of a pharmacological agent from a polymeric material. Eluting may also refer to the release of a material from a substrate via diffusional mechanisms or by release from a polymeric material/substrate as a result of the breakdown or erosion of the material/substrate.

[0021] The term "erodible" as used herein refers to the ability of a material to maintain its structural integrity for a desired period of time, and thereafter gradually undergo any of, numerous processes whereby the material substantially loses tensile strength and mass. Examples of such processes comprise enzymatic and non-enzymatic hydrolysis, oxidation, enzymatically-assisted oxidation, and others, thus including bioresorption, dissolution, and mechanical degradation upon interaction with a physiological environment into components that the patient's tissue can absorb, metabolize, respire, and/or excrete. The terms "erodible" and "degradable" are intended to be used herein interchangeably.

[0022] The term "dosage regimen" is used herein to describe both exogenously administered and internally administered pharmacological agents. A dosage regimen includes both an amount of a pharmacological agent and time(s) that each dose is to be taken. A dosage regimen may also indicate whether a pharmacological agent is to be taken with food or not, and whether other pharmacological agents are to be avoided. A dosage regimen may also indicate the designed rate at which a pharmaceutical agent is released from a substrate.

[0023] The term "everolimus" is used herein to mean any member of the inacrolide family of pharmacological agents.

[0024] The term "hydrophobic" is used herein to mean not soluble in water.

[0025] The term "hydrophilic" is used herein to mean soluble in water.

[0026] The term "lumen" is used herein to mean any inner open space or cavity of a body passageway.

[0027] The terms "polymer" and "polymeric material" are synonymous and are to be broadly construed to include, but not be limited to, homopolymers, copolymers, terpolymers, and the like.

[0028] The term "prosthesis" is used herein in a broad sense to denote any type of intraluminal prosthesis, endoprosthesis, or other device which is implanted in the body of a subject for some therapeutic reason or purpose including, but not limited to stents, drug delivery devices, etc.

[0029] The term "subject" is used herein to describe both human beings and animals (e.g., mammalian subjects) for medical, veterinary, testing and/or screening purposes.

[0030] As used herein, phrases such as "between X and Y" and "between about X and Y" should be interpreted to include X and Y.

[0031] As used herein, phrases such as "between about X and Y" mean "between about X and about Y."

[0032] As used herein, phrases such as "from about X to Y" mean "from about X to about Y."

[0033] Embodiments of the present invention can be employed in conjunction with a number of manufacturing processes associated with producing intraluminal prostheses including, but not limited to, extrusion, pultrusion, injection molding, compression molding, etc. Moreover, embodiments of the present invention may be utilized in batch, semicontinuous, and/or continuous manufacturing processes.

[0034] Referring now to **FIG. 1**, an intraluminal prosthesis **10**, that may be produced according to embodiments of the present invention, is illustrated. The illustrated prosthesis **10** is a stent and includes a tubular body portion **12** having a first end **14**, a second end **16**, and a flow passage **18** defined therethrough from the first end **14** to the second end **16**. The body portion **12** is sized for intraluminal placement within the vasculature of a subject and is expandable from a first, reduced cross-sectional dimension (i.e., contracted configuration) to a second enlarged cross-sectional dimension (i.e., expanded configuration) so that the body portion **12** can be transported intraluminally to a treatment site and then expanded to the second enlarged cross-sectional dimension so as to engage and support the vascular wall at the treatment site.

[0035] The body portion **12** is formed at least in part from an erodible, polymeric material and/or a coating of erodible, polymeric material. One or more portions of the body portion **12** may be formed from non-erodible material and/or a coating of non-erodible material. The polymeric material may comprise polymers oriented uniaxially and/or biaxially. Exemplary erodible materials that may be utilized in accordance with embodiments of the present invention include, but are not limited to, surgical gut, silk, cotton, poly(hydroxybutyrate), polycarbonates, polyacrylates, polyanhydrides, poly(ortho esters), poly(phosphoesters), polyesters, polyamides (such as polyamides derived from D-glucose), polyphosphazenes, poly(p-dioxane), poly(amino acid), polyglactin, and copolymers thereof, erodable hydrogels, natural polymers such as collagen and chitosan, etc. See, e.g., U.S. Pat. No. 5,723,508 to Healy et al. Particular examples of suitable erodible polymers include, but are not limited to, aliphatic polyester polymers such as poly(lactic acid), poly(L-lactic acid), poly(D,L-lactic acid), poly(glycolic acid), poly(D-lactic-co-glycolic acid), poly(L-lactic-co-glycolic acid), poly(D,L-lactic-co-glycolic acid), poly(ε-caprolactone), poly(valerolactone), poly(hydroxy butyrate) (including poly(hydroxy butyrate valerate)), poly(hydrovalerate), polydioxanone, poly(propylene fumarate), etc., including copolymers thereof such as polylactic acid-polyethylene glycol block copolymer, and poly(ethyleneoxide)-poly(butylenetetraphthalate), poly(lactic acid-co-trimethylene carbonate), poly(lactic acid-co-lysine), poly(ε-caprolactone copolymers), poly(L-lactic acid copolymers), etc. See, e.g., J. Oh et al., PCT Application WO 99/59548 at page 2. Additional examples of erodible polymers are set forth in U.S. Pat. No. 5,916,585 to Cook et al., which is incorporated herein by is reference in its entirety. The molecular weight (that is, average molecular weight) of the polymer may be from. 1,000, 10,000, 100,000 or 500,000 to 2,000,000 or 4,000,000 Daltons, or more.

[0036] According to embodiments of the present invention, one or more pharmacological agents (represented by stippling **15**) may be infused within the erodible, polymeric material **13** of the body portion **12**, or within an erodible coating surrounding the body portion **12**, or portions thereof. The body portion material **13** and/or coating is configured to allow the one or more pharmacological agents **15** infused therein to elute, preferably at a predetermined, controlled rate.

[0037] Pharmacological agents suitable for inclusion in prosthesis materials and/or coatings, according to embodiments of the present invention include, but are not limited to, drugs and other biologically active materials, and may be intended to perform a variety of functions, including, but not limited to: anti-cancer treatment (e.g., Resan), anti-clotting or anti-platelet formation, the prevention of smooth muscle cell growth and migration on a vessel wall, and cell cycle inhibitors. Pharmacological agents may include antineoplastics, antimitotics, antiinflammatories, antiplatelets, anticoagulants, antifibrins, antithrombins, antiproliferatives, antibiotics, antioxidants, immunosuppressives, and antiallergic substances as well as combinations thereof. Examples of such antineoplastics and/or antimitotics include paclitaxel (e.g., TAXOL® by Bristol-Myers Squibb Co., Stamford, Conn.), docetaxel (e.g., TAXOTERE® from Aventis S. A., Frankfurt, Germany) methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, doxorubicin hydrochloride (e.g., ADRIAMYCIN®from Pharmacia & Upjohn, Peapack N.J.), and mitomycin (e.g., MUTAMYCIN® from Bristol-Myers Squibb Co., Stamford, Conn.). Examples of such suitable antiinflammatories include glucocorticoids such as dexamethasone, methylprednisolone, hydrocortisone and betamethasone and non-steroidal antiinflammatories such as aspirin, indomethacin and ibuprofen. Examples of such antiplatelets, anticoagulants, antifibrin, and antithrombins include sodium heparin, low molecular weight heparins, heparinoids, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogues, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor

antagonist antibody, recombinant hirudin, and thrombin inhibitors such as ANGIOMAX™ (Biogen, Inc., Cambridge, Mass.) Examples of such cytostatic or ant iproliferative agents include actinomycin D as well as derivatives and analogs thereof (manufactured by Sigma-Aldrich, Milwaukee, Wis.; or COSMEGEN®available from Merck & Co., Inc., Whitehouse Station, N.J.), angiopeptin, angiotensin converting enzyme inhibitors such as captopril (e.g., CAPOTEN® and CAPOZIDE® from Bristol-Myers Squibb Co., Stamford, Conn.), cilazapril or lisinopril (e.g., Prinivilo and PRINZIDE® from Merck & Co., Inc., Whitehouse Station, N.J.); calcium channel blockers (such as nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), histamine antagonists, lovastatin (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug, brand name MEVACOR® from Merck & Co., Inc., Whitehouse Station, N.J.), monoclonal antibodies (such as those specific for Platelet-Derived Growth Factor (PDGF) receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitors, suramin, serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. An example of an antiallergic agent is permirolast potassium. Other therapeutic substances or agents that may be used include alphainterferon, genetically engineered epithelial cells, and dexamethasone.

[0038] According to embodiments of the present invention, other agents, such as heat sensitive biologics (e.g., transfection vectors, genetic material, tissue material, etc.) may be infused within the erodible polymeric material **13** of the body portion **12**, or within an erodible coating surrounding the body portion **12**, or portions thereof.

[0039] U.S. Pat. No. 4,994,033 to Shockey et al.; U.S. Pat. No. 5,674,192 to Sahatian et al. and U.S. Pat. No. 5,545,208 to Wolff et al. disclose catheters comprising absorbable/biodegradable polymers or hydrogels containing the desired dosage of a drug. Stents incorporating drug delivery may be found, for example, in U.S. Pat. No. 5,766,710 to Turnlund et al.; U.S. Pat. No. 5,769,883 to Buscemi et al.; U.S. Pat. No. 5,605,696 to Eury et al.; U.S. Pat. No. 5,500,013 to Buscemi et al.; U.S. Pat. No. 5,551,954 to Buscemi et al. and U.S. Pat. No. 5,443,458 to Eury, each of which is incorporated herein by reference in its entirety.

[0040] If a plurality of pharmacological agents are utilized, the plurality of pharmacological agents may be homogeneously distributed on the body portion **12**, or heterogeneously distributed on the body portion **12**.

[0041] According to embodiments of the present invention, a release agent (represented by cross-hatching **30**) may be coated on the body portion **12** or incorporated within the body portion **12**. The release agent **30** is configured to release a pharmacological agent **15** in a predetermined manner. Multiple release agents may be utilized. For example, if multiple pharmacological agents are utilized, multiple release agents may be utilized.

[0042] Referring now to **FIG. 2**, methods of manufacturing polymeric intraluminal prostheses (e.g., stents, drug delivery devices, etc.) include annealing the polymeric material to selectively modify the crystallinity thereof (Block **100**). The term "selectively" is used herein to indicate that a physical property of the polymeric material of an intraluminal prosthesis can be accurately controlled and modified to specific parameters via annealing. Annealing may include heating the polymeric material to a temperature between the glass transition temperature and the melting temperature (i.e., $T_g<T_{anneal}<T_m$) of the polymeric material for a period of time sufficient to selectively increase the crystallinity of the polymeric material (Block **200**).

[0043] An exemplary polymeric material for intraluminal prostheses according to embodiments of the present invention may have a melting temperature between about 173° C.-178° C. and a glass transition temperature of between about 60° C.-65° C. However, embodiments of the present invention are not limited to polymeric materials with melting temperatures and glass transition temperatures in these ranges. Polymeric materials having various other melting temperatures and glass transition temperatures can be used, without limitation.

[0044] Annealing may include initially heating the polymeric material to a temperature that is higher than the melting temperature (i.e., $T_{anneal}>T_m$) of the polymeric material for a period of time and then quenching the polymeric material to a temperature that is lower than the melting temperature (i.e., $T_{quench}<T_m$) for a period of time sufficient to selectively control (i.e., limit the extent of or control the quality or nature of) the crystallinity of the polymeric material (Block **300**). According to embodiments of the present invention, the quench temperature may be between the glass transition temperature and the melting temperature of the polymeric material (i.e., $T_g<T_{qench}<T_m$). According to embodiments of the present invention, the quench temperature may be lower than the glass transition temperature of the polymeric material (i.e., $T_{quench}<T_g$).

[0045] Referring to **FIG. 3**, annealing to modify crystallinity may be utilized to selectively modify various properties of the polymeric material of an intraluminal prosthesis. For example, annealing may include heating the polymeric material to a temperature between the glass transition temperature and the melting temperature (i.e., $T_g<T_{anneal}<T_m$) of the polymeric material for a period of time sufficient to: selectively increase or decrease the modulus of the polymeric material (Block **202**); selectively increase or decrease the hoop strength of the intraluminal prosthesis (Block **204**); selectively modify the elution rate (increase or decrease) of a pharmacological agent subsequently disposed on or within the annealed polymeric material (Block **206**); selectively increase or decrease stress in the intraluminal prosthesis (Block **208**); and selectively modify the polymeric material such that it erodes at a different rate (i.e., slower or faster) (Block **210**).

[0046] As is known to those skilled in the art, a change in polymer crystallization is an important way to modify physical properties of polymer materials. The degree and nature of crystallization can have noticeable effects on the physical properties of polymer materials. As used herein, "degree of crystallization" refers to the total amount of crystallinity of a polymer (e.g., as determined by wide angle x-ray scattering (WAXS) or by differential scanning calorimetry (DSC)). As used herein, "nature of crystallization" refers to the exact morphology of crystallites., whether they are large crystallites or small crystallites, or some specific morphology such as spherulitic, elongated, deformed, line nucleated, or a "shish-ka-bob" type structure or some other morphology, at the same overall degree of crystallinity.

[0047] The state of order of polymers can extend from the completely random (amorphous) to the completely ordered

(perfect crystal). The physical structures that are found depend not only on the configuration and conformation of the molecules, but also by the experimental conditions with which the polymers that make up the intraluminal device or the coating on the intraluminal device were exposed to. Crystallinity is strongly influenced by the crystallization conditions and it includes frozen in, non-equilibrium states. The crystallization conditions, however, will not only influence the overall amount of crystallinity, but it will also influence the detailed morphology of the sample.

[0048] Essentially all polymers exhibit a necking effect on stretching within a specific temperature region. The effect can be recognized by the formation of a neck during elongation due to the occurrence of a constriction after the upper flow limit is reached. The cross section of this constriction continues to decrease up to the lower flow limit. With continued elongation, the cross section of this constriction remains practically constant, but the length of the constricted portion continues to increase at the expense of the rest of the sample. It is sometimes desirable to manufacture intraluminal devices, such as stents, out of precursor stock material that is unoriented. It is sometimes desirable to manufacture intraluminal devices, such as stents, out of precursor stock material that is uniaxially oriented. It is sometime desirable to manufacture intraluminal devices, such as stents, out of precursor stock material that is biaxially oriented. Stents can be oriented or stretched upon deployment using balloon techniques. The degree and nature of the orientation can affect: the mechanical properties of the intraluminal device or the coating on the intraluminal device; the elution profile of the drug or drugs infused within it or coated onto it; and the biodegradation or bioabsorption of the intraluminal device or the coating on the intraluminal device.

[0049] Examples of uniaxial orientation include, but are not limited to, 1x-4x, where "x" equals the axial dimension of the original specimen. Examples of biaxial orientation include, but are not limited to, 4x:1x, 3x:2x, where "x" equals the pre-oriented dimension of the specimen, and where "#x" equals the end dimension of the specimen post-orientation. Biaxial implies application of a deforming load in two dimensions, each perpendicular to the other.

[0050] The crystallinity of partially crystalline polymers during elongation can increase, decrease, or remain constant. Chain orientation, on the other hand, increases continuously during elongation. With thermally quenched samples having a low degree of crystallinity, the available crystallites are first oriented in the stress direction. The amorphous regions can then crystallize. Annealed polymers, however, can be more highly crystalline. The stress-strain diagrams of stretched polymers differ significantly from those of unstretched polymers. The absence of an upper flow limit, that is the absence of cold flow, is common.

[0051] Polymeric materials that have higher degrees of crystallinity and chain orientation can have a higher modulus, which may be useful to increase the hoop strength of polymeric intraluminal devices, such as stents. As is known to those skilled in the art, modulus is a measure of how well a material resists deformation, and is measured by calculating stress and dividing by elongation. Upon deployment using angioplasty balloons, polymeric stents can be stretched, the degree of stress that builds up upon stretching will be influenced by the degree of crystallinity and the orientation of the polymeric chains relative to the orientation of the stretching during deployment.

[0052] In addition to affecting the mechanical properties, the degree and nature of the crystallinity in a sample can play a significant role in modifying the elution profile of a drug infused within the sample as well as influence the rate of absorption or degradation of the polymeric stent or the polymeric coating on a stent.

[0053] According to embodiments of the present invention, crystallinity of polymeric intraluminal prostheses can be increased from about 30% to about 70% or greater. This increase in crystallinity reduces permeability by both reducing solubility and increasing the tortuosity of the diffusional pathway. Increasing crystallinity and orienting (uniaxially or biaxially) crystallites also improves mechanical properties including radial compressive strength and flexibility.

[0054] Referring back to **FIG. 2**, annealing may be performed in the presence of carbon dioxide (Block **400**). According to other embodiments of the present invention, annealing may be preceded by immersing the polymeric material in carbon dioxide (Block **500**).

[0055] According to embodiments of the present invention, annealing may be performed in the presence of a nucleating agent disposed on or within the polymeric material (Block **600**). As known to those skilled in the art, nucleating agents are chemical substances which when incorporated in polymer materials form nuclei for the growth of crystals in the polymer melt. For example, in certain polymers, a higher degree of crystallinity and more uniform crystalline structure may be obtained by adding a nucleating agent.

[0056] According to other embodiments of the present invention, molecular crosslinking of the polymeric material may be modified by subjecting the polymeric material to chemical treatment and/or irradiation (Block **700**). The polymeric material may be subjected to chemical treatment and/or irradiation before, during and/or after annealing. Crosslinking can impact the degree and nature of elution of pharmacological agents from an intraluminal prosthesis by increasing the tortuosity of the diffusional pathway and by slowing down the erosion rate of the prosthesis. Moreover, crosslinking can impact the deployment and/or deformation characteristics during deployment of an intraluminal prosthesis. Crosslinking can also impact the degree and nature of biodegration/bioabsorption characteristics of a polymeric intraluminal prosthesis.

[0057] Subjecting the polymeric material to chemical treatment (Block **700**) may include subjecting the polymeric material to multifunctional cross-linking agents such as formaldehyde, difunctional dialdehyde, and diisocyantes. Subjecting the polymeric material to chemical treatment may include subjecting the polymeric material to enzymatic cross-linking agents such as polyethylene glycols (PEG) functionalized with a glutaminamide and a lysine-containing polypeptide using a natural tissue enzyme, and transglutaminase.

[0058] Subjecting the polymeric material to irradiation (Block **700**) may include subjecting the polymeric material to ionizing radiation such as e-beam irradiation or gamma irradiation. These procedures may be done in concert as a

sterilization step. UV/visible irradiation may be utilized with additives such as sensitizers and/or photoacid generators. Typical photoacid generators include dinitrobenzyltosylates, sulfonium salts, iodonium salts, diazodisulfone derivatives and sulfonates, etc. and are available from sources such as Wako Chemicals USA, Inc., 1600 Bellwood Road, Richmond, Va. 23237 USA.

[0059] Referring to **FIG. 4**, methods of impregnating annealed polymeric intraluminal prostheses with one or more pharmacological agents (Block **800**) are illustrated. According to embodiments of the present invention, an intraluminal prosthesis is immersed in a mixture of carrier fluid and pharmacological agent(s) (Block **810**). One or more pharmacological agents may be infused within the annealed polymeric material of an intraluminal prosthesis or within an annealed polymeric coating surrounding an intraluminal prosthesis.

[0060] The carrier fluid may be a gas, liquid, or supercritical fluid. The carrier fluid may be heterogeneous or homogeneous in composition, i.e., may be a single phase composition or contain one or more additional phases., such as in the form of a microemulsion, emulsion, dispersion, suspension, etc. The carrier fluid may comprise, consist of, or consist essentially of carbon dioxide. Where multiple phases are found in the carrier fluid, carbon dioxide may be the continuous phase. One or more other ingredients may be included in the carrier fluid, such as co-solvents (i.e., water or organic co-solvents such as ethanol and methanol), surfactants or the like may be included. Where one or more organic co-solvents are included, it or they may be polar or nonpolar (or at least one of each). Where one or more surfactants are included it or they may comprise a carbon dioxide-philic group coupled to either a lipophilic (hydrophobic) or hydrophilic group, a conventional surfactant comprising a liphophilic (hydrophobic) group coupled to a hydrophilic group, or one or more of each. The carrier fluid may comprise at least 30, 40, 50, 60, 70, 80 or 90 percent by weight of carbon dioxide. When water is present in the carrier fluid, the water may comprise from about 0.01, 0.1, or 0.5 to about 1, 5, 10 or 20 percent by weight of the composition, or more.

[0061] If a plurality of pharmacological agents are utilized, the plurality of pharmacological agents may be homogeneously distributed on and/or within the intraluminal prosthesis polymeric material, or heterogeneously distributed on and/or within the intraluminal prosthesis polymeric material.

[0062] Pharmacological agents, according to embodiments of the present invention, may be hydrophilic or hydrophobic. For hydrophilic pharmacological agents, the carrier fluid may be water. For hydrophobic pharmacological agents, the carrier fluid may be a supercritical fluid, such as carbon dioxide, or it may be a liquefied gas such as carbon dioxide, CFC, HCFL, etc. An exemplary hydrophobic pharmacological agent according to embodiments of the present invention is everolimus. Everolimus is a proliferation inhibitor that targets primary causes of chronic rejection in organ transplantation patients and may also be effective for the prevention of restenosis.

[0063] According to embodiments of the present invention, carbon dioxide may be employed as a fluid in a liquid, gaseous, or supercritical phase. If liquid carbon dioxide is used, the temperature employed during the process is typically below 31° C. If gaseous carbon dioxide is used, the phase may be employed at high pressure. As used herein, the term "high pressure" generally refers to carbon dioxide having a pressure from about 50 to about 500 bar. Carbon dioxide may be utilized in a "supercritical" phase. As used herein, the term "supercritical" means that a fluid medium is above its critical temperature and pressure, i.e., about 31° C. and about 71 bar for carbon dioxide. The thermodynamic properties of carbon dioxide are reported in Hyatt, J. Org. Chem. 49: 5097-5101 (1984), and are well known to those skilled in the art.

[0064] Typically, supercritical fluids are gases at ambient temperature and pressure. However, when maintained at or above its critical point, a supercritical fluid displays properties of both a gas and a liquid. In particular, a supercritical fluid has the solvent characteristics of a liquid, but the low surface tension of a gas. Accordingly, as with a gas, a supercritical fluid can more readily diffuse into polymeric material. While any of a variety of supercritical fluids may be utilized in accordance with embodiments of the present invention, carbon dioxide is a particularly desirable supercritical fluid because it is substantially non-reactive and nontoxic (i.e., inert).

[0065] Carbon dioxide is non-toxic, non-flammable, chemically inert, completely recoverable, abundant and inexpensive. Carbon dioxide has properties that are between those of many liquids and gases. At room temperature and above its vapor pressure, carbon dioxide exists as a liquid with a density comparable to organic solvents but with excellent wetting properties and a very low viscosity. Above its critical temperature and pressure (31° C. and 71 bar), carbon dioxide is in the supercritical state and has gas-like viscosities and liquid-like densities. Small changes in temperature or pressure cause dramatic changes in the density, viscosity, and dielectric properties of supercritical carbon dioxide, making it an unusually tunable, versatile, and selective solvent.

[0066] Still referring to **FIG. 4**, the mixture of carrier fluid and pharmacological agent is pressurized for a time sufficient to cause the polymeric material of the intraluminal prosthesis to swell such that the carrier fluid and pharmacological agent at least partially penetrate the swollen polymeric material (Block, **820**). According to embodiments of the present invention, pressure can be added by the use of pressurized carbon dioxide, or by the use of a different second pressurized gas. A different second pressurized gas, such as one or more inert gases, may be helium, nitrogen, argon, etc., or combinations thereof.

[0067] For pharmacological agents soluble in carbon dioxide (e.g., hydrophobic agents), carbon dioxide may be utilized as both the carrier fluid and the pressurizing medium. For pharmacological agents not soluble in carbon dioxide (e.g., hydrophilic agents), the pharmacological agent and carrier fluid may be pressurized by an overlying blanket of carbon dioxide. Carbon dioxide is well known to those skilled in the art to be capable of swelling and plasticizing polymeric materials. Carbon dioxide is capable of partitioning into polymeric materials that are in its presence. When this occurs it can dramatically lower the glass transition temperature of the amorphous phase of the polymer. When this occurs, the diffusivity of a third com-

ponent can increase dramatically. Such plasticization can enable the partitioning of third components, like a pharmaceutical agent, into the polymeric material. Conventionally, heat is required to increase glass transition temperature. Unfortunately, heating can be damaging to pharmaceutical agents that are thermally labile.

[0068] Pressure is then removed such that the carrier fluid diffuses out of the swollen polymeric material and such that a predetermined amount of the pharmacological agent remains elutably trapped within the polymeric material (Block **830**). The term "elutably trapped" means that the pharmacological agent is disposed within the polymeric material in such a way that it can elute (at a predetermined rate) therefrom when the intraluminal prosthesis is deployed within the body of a subject.

[0069] The step of removing pressure (Block **830**) is carried out under controlled conditions after a predetermined time and according to a predetermined schedule to insure that the desired predetermined amount of the pharmacological agent(s) remains. Controlled conditions include controlling one or more of the following parameters in a predetermined pattern: temperature, rate of temperature change, pressure, rate of pressure change, carrier fluid quantity, concentration of the pharmacological agent in the carrier fluid, etc. Loading a polymeric intraluminal prosthesis, such as a stent, or a polymeric coating on an intraluminal prosthesis can be from 0.0001 wt % to 30 wt %. However, loading at higher weight-percentages are possible (i.e., >30 wt %). These parameters can control the concentration of the pharmacological agent(s) entrapped within the polymeric material after depressurization has been achieved. Moreover, as these parameters are varied, concentration gradients of the pharmacological agent(s) entrapped within the polymeric material after depressurization can be achieved. Such concentration gradients can give rise to modified elution profiles of the pharmacological agent(s).

[0070] Embodiments of the present invention described above may be carried out using apparatus known to those skilled in the art. An exemplary apparatus for use in impregnating intraluminal prostheses with pharmacological agents is illustrated and described in U.S. Pat. No. 5,808,060 to Perman et al., which is incorporated herein by reference in its entirety.

[0071] Selective annealing may be performed so as to selectively increase (or vary) crystallinity of one or more isolated portions of the polymeric material of an intraluminal prosthesis. This will allow for customization of intraluminal prostheses and allow for matching to anatomical and physiological environments. For example, crystallinity can be increased in a mid section of an intraluminal prosthesis to enhance mechanical strength and scaffolding capability thereof, while leaving the ends of the intraluminal prosthesis more compliant so as to match the physical compliance of the non-diseased vessel wall.

[0072] According to embodiments of the present invention, selective annealing may be performed by applying a mask to one or more portions of an intraluminal prosthesis. The mask acts as a barrier to carbon dioxide absorption, thereby allowing non-masked portions to absorb carbon dioxide and to be crystallized thereby. According to other embodiments of the present invention, selective annealing may be performed by only heating selected areas of an intraluminal prosthesis. For example, a light source or a mild laser may be utilized to heat selected areas of an intraluminal prosthesis. According to other embodiments of the present invention, selective annealing may be performed by adding chemical crosslink agents only to certain areas of the polymeric material of an intraluminal prosthesis.

[0073] According to other embodiments of the present invention, selective annealing may be performed by selectively subjecting the polymeric material of an intraluminal prosthesis to irradiation, such as e-beam irradiation and gamma irradiation.

[0074] Intraluminal prostheses provided in accordance with embodiments of the present invention may be employed in sites of the body other than the vasculature including, but not limited to, biliary tree, esophagus, bowels, tracheo-bronchial tree, urinary tract, organs, etc.

[0075] The foregoing is illustrative of the present invention and is not to be construed as limiting thereof. Although a few exemplary embodiments of this invention have been described, those skilled in the art will readily appreciate that many modifications are possible in the exemplary embodiments without materially departing from the novel teachings and advantages of this invention. Accordingly, all such modifications are intended to be included within the scope of this invention as defined in the claims. The invention is defined by the following claims, with equivalents of the claims to be included therein.

That which is claimed is:

1. A method of manufacturing an intraluminal prosthesis having an outer surface of polymeric material, wherein the intraluminal prosthesis is expandable from a contracted configuration when deployed within a lumen of a subject body, the method comprising annealing the polymeric material for a time prior to deployment and at a temperature sufficient to selectively modify the crystallinity thereof.

2. The method of claim 1, wherein annealing comprises heating the polymeric material to a temperature between the glass transition temperature and the melting temperature of the polymeric material for a period of time sufficient to selectively increase the crystallinity of the polymeric material.

3. The method of claim 1, wherein annealing comprises heating the polymeric material to a first temperature higher than the melting temperature of the polymeric material for a first period of time and then quenching the polymeric material to a second temperature lower than the melting temperature for a second period of time sufficient to selectively control the crystallinity of the polymeric material.

4. The method of claim 3, wherein the second temperature is between the glass transition temperature and the melting temperature of the polymeric material.

5. The method of claim 3, wherein the second temperature is lower than the glass transition temperature of the polymeric material.

6. The method of claim 1, wherein annealing comprises heating the polymeric material to a temperature between the glass transition temperature and the melting temperature of the polymeric material for a period of time sufficient to selectively increase or decrease the modulus of the polymeric material.

7. The method of claim 1, wherein annealing comprises heating the polymeric material to a temperature between the

glass transition temperature and the melting temperature of the polymeric material for a period of time sufficient to selectively increase or decrease the hoop strength of the intraluminal prosthesis.

8. The method of claim 1, wherein annealing comprises heating the polymeric material to a temperature between the glass transition temperature and the melting temperature of the polymeric material for a period of time sufficient to selectively modify an elution rate of a pharmacological agent subsequently elutably trapped within the polymeric material.

9. The method of claim 1, wherein annealing comprises heating the polymeric material to a temperature between the glass transition temperature and the melting temperature of the polymeric material for a period of time sufficient to selectively affect heat sensitive agents within the polymeric material.

10. The method of claim 8, wherein the elution rate is increased.

11. The method of claim 8, wherein the elution rate is decreased.

12. The method of claim 1, wherein annealing comprises heating the polymeric material to a temperature between the glass transition temperature and the melting temperature of the polymeric material for a period of time sufficient to selectively decrease stress in the intraluminal prosthesis.

13. The method of claim 1, wherein annealing comprises heating the polymeric material to a temperature between the glass transition temperature and the melting temperature of the polymeric material for a period of time sufficient to selectively increase stress in the intraluminal prosthesis.

14. The method of claim 1, wherein the polymeric material is configured to erode at a first rate when deployed within a lumen of a subject body, and wherein annealing comprises heating the polymeric material to a temperature between the glass transition temperature and the melting temperature of the polymeric material for a period of time sufficient to selectively modify the polymeric material such that it erodes at a second rate that is greater than the first rate when deployed within a lumen of a subject body.

15. The method of claim 1, wherein the polymeric material is configured to erode at a first rate when deployed within a lumen of a subject body, and wherein annealing comprises heating the polymeric material to a temperature between the glass transition temperature and the melting temperature of the polymeric material for a period of time sufficient to selectively modify the polymeric material such that it erodes at a third rate that is less than the first rate when deployed within a lumen of a subject body.

16. The method of claim 1, wherein annealing is performed in the presence of carbon dioxide.

17. The method of claim 1, wherein annealing is preceded by immersing the polymeric material in carbon dioxide.

18. The method of claim 1, wherein annealing is performed in the presence of a nucleating agent disposed on or within the polymeric material.

19. The method of claim 1, further comprising modifying molecular crosslinking of the polymeric material by subjecting the polymeric material to chemical treatment.

20. The method of claim 19, wherein subjecting the polymeric material to chemical treatment comprises subjecting the polymeric material to one or more multifunctional cross-linking agents.

21. The method of claim 20, wherein the one or more multifunctional cross-linking agents are selected from the group consisting of formaldehyde, difunctional dialdehyde, and diisocyantes.

22. The method of claim 21, wherein subjecting the polymeric material to chemical treatment comprises subjecting the polymeric material to one or more enzymatic crosslinking agents.

23. The method of claim 22, wherein the one or more enzymatic crosslinking agents are selected from the group consisting of polyethylene glycols (PEG) functionalized with a glutaminamide and a lysine-containing polypeptide using a natural tissue enzyme, and transglutaminase.

24. The method of claim 19, wherein the polymeric material is subjected to chemical treatment during annealing.

25. The method of claim 19, wherein the polymeric material is subjected to chemical treatment after annealing.

26. The method of claim 1, further comprising modifying molecular crosslinking of the polymeric material by subjecting the polymeric material to irradiation.

27. The method of claim 1, further comprising sterilizing the polymeric material by subjecting the polymeric material to irradiation.

28. The method of claim 26, wherein radiation utilized to modify molecular crosslinking is selected from the group consisting of ionizing radiation and UV/visible radiation.

29. The method of claim 27, wherein-ionizing irradiation comprises e-beam irradiation or gamma irradiation.

30. The method of claim 26, wherein radiation utilized to modify molecular crosslinking comprises UV/visible radiation in the presence of a photoacid generator.

31. The method of claim 30, wherein the photoacid generator is selected from the group consisting of dinitrobenzyltosylates, sulfonium salts, iodonium salts, diazodisulfone derivatives and sulfonates.

32. The method of claim 26, wherein the polymeric material is subjected to irradiation during annealing.

33. The method of claim 26, wherein the polymeric material is subjected to irradiation after annealing.

34. The method of claim 1, wherein the intraluminal prosthesis is a stent.

35. The method of claim 1, wherein the polymeric material is erodible.

36. The method of claim 1, wherein the polymeric material is non-erodible.

37. The method of claim 1, wherein the polymeric material is a coating on the intraluminal prosthesis.

38. The method of claim 36, wherein the erodible polymeric material is selected from the group consisting of, surgical gut, silk, cotton, poly(hydroxybutyrate), polycarbonate, polyacrylate, polyanhydride, poly(ortho esters), poly(phosphoesters), polyesters, polyamides, polyphosphazenes, poly(p-dioxane), poly(amino acid), polyglactin, erodable hydrogels, collagen, chitosan, poly(lactic acid), poly(L-lactic acid), poly(D,L-lactic acid), poly(glycolic acid), poly(D-lactic-co-glycolic acid), poly(L-lactic-co-glycolic acid), poly(D,L-lactic-co-glycolic acid), poly(ε-caprolactone), poly(valerolactone), poly(hydroxy butyrate), poly(hydrovalerate), polydioxanone, poly(propylene fumarate), poly(ethyleneoxide)-poly(butylenetetraphthalate), poly(lactic acid-co-lysine), poly(lactic acid-co-trimethylene carbonate), poly(L-lactic acid) and poly(ε-caprolactone) copolymers.

39. The method of claim 36, wherein the erodible polymeric material comprises a blend of polymeric material selected from the group consisting of, surgical gut, silk, cotton, poly(hydroxybutyrate), polycarbonate, polyacrylate, polyanhydride, poly(ortho esters), poly(phosphoesters), polyesters, polyamides, polyphosphazenes, poly(p-dioxane), poly(amino acid), polyglactin, erodable hydrogels, collagen, chitosan, poly(lactic acid), poly(L-lactic acid), poly(D,L-lactic acid), poly(glycolic acid)., poly(D-lactic-co-glycolic acid), poly(L-lactic-co-glycolic acid), poly(D,L-lactic-co-glycolic acid), poly(ϵ-caprolactone), poly(valerolactone), poly(hydroxy butyrate), poly(hydrovalerate), polydioxanone, poly(propylene fumarate), poly(ethyleneoxide)-poly(butylenetetraphthalate), poly(lactic acid-co-lysine), poly(lactic acid-co-trimethylene carbonate), poly(L-lactic acid) and poly(ϵ-caprolactone) copolymers.

40. The method of claim 1, further comprising the step of impregnating the polymeric material with a predetermined amount of a pharmacological agent after annealing.

41. The method of claim 40, wherein impregnating the polymeric material with a predetermined amount of a pharmacological agent comprises:

immersing the intraluminal prosthesis in a mixture of a carrier fluid and a pharmacological agent;

pressurizing the mixture for a time sufficient to cause the polymeric material to swell such that the carrier fluid and pharmacological agent at least partially penetrate the swollen polymeric material; and

removing the pressure such that the carrier fluid diffuses out of the swollen polymeric material and such that a predetermined amount of the pharmacological agent remains elutably trapped within the polymeric material.

42. The method of claim 40, wherein the carrier fluid is carbon dioxide, and wherein the pharmacological agent is hydrophobic.

43. The method of claim 42, wherein the pharmacological agent is selected from the group consisting of antineoplastics, antimitotics, antiinflammatories, antiplatelets, anticoagulants, antifibrins, antithrombins, antiproliferatives, antibiotics, antioxidants, immunosuppressives, antiallergic substances, and combinations thereof.

44. The method of claim 40, wherein the carrier fluid is water, and wherein the pharmacological agent is hydrophilic.

45. The method of claim 44, wherein pressurizing the mixture of carrier fluid and pharmacological agent comprises subjecting the mixture of carrier fluid and pharmacological agent to pressurized carbon dioxide.

46. The method of claim 42, wherein the carbon dioxide is present in a supercritical state.

47. The method of claim 46, wherein the carbon dioxide contains a co-solvent.

48. The method of claim 47, wherein the co-solvent is selected from the group consisting of ethanol and methanol.

49. The method of claim 1, wherein annealing the polymeric material comprises selectively modifying the crystallinity of only a portion of the polymeric material.

50. The method of claim 49, wherein selectively modifying the crystallinity of only a portion of the polymeric material:

masking one or more portions of the polymeric material; and

subjecting exposed portions of the polymeric material to carbon dioxide.

51. The method of claim 49, wherein selectively modifying the crystallinity of only a portion of the polymeric material comprises heating a portion of the polymeric material to a temperature between the glass transition temperature and the melting temperature of the polymeric material.

52. The method of claim 49, wherein selectively modifying the crystallinity of only a portion of the polymeric material comprises subjecting a portion of the polymeric material to chemical treatment.

53. The method of claim 49, wherein selectively modifying the crystallinity of only a portion of the polymeric material comprises subjecting a portion of the polymeric material to irradiation.

54. An intraluminal prosthesis, comprising a tubular body having an outer surface of polymeric material, wherein the tubular body is expandable from a contracted configuration when deployed within a lumen of a subject body, wherein the polymeric material is annealed for a time prior to deployment and at a temperature sufficient to selectively modify the crystallinity thereof.

55. The intraluminal prosthesis of claim 54, wherein the polymeric material is heated to a temperature between the glass transition temperature and the melting temperature of the polymeric material for a period of time sufficient to selectively increase the crystallinity of the polymeric material.

56. The intraluminal prosthesis of claim 54, wherein the polymeric material is heated to a first temperature higher than the melting temperature of the polymeric material for a first period of time and then quenched to a second temperature lower than the melting temperature for a second period of time sufficient to selectively control the crystallinity of the polymeric material.

57. The intraluminal prosthesis of claim 56, wherein the second temperature is between the glass transition temperature and the melting temperature of the polymeric material.

58. The intraluminal prosthesis of claim 56, wherein the second temperature is lower than the glass transition temperature of the polymeric material.

59. The intraluminal prosthesis of claim 54, wherein the polymeric material is heated to a temperature between the glass transition temperature and the melting temperature of the polymeric material for a period of time sufficient to selectively increase or decrease the modulus of the polymeric material.

60. The intraluminal prosthesis of claim 54, wherein the polymeric material is heated to a temperature between the glass transition temperature and the melting temperature of the polymeric material for a period of time sufficient to selectively increase or decrease the hoop strength of the intraluminal prosthesis.

61. The intraluminal prosthesis of claim 54, wherein a pharmacological agent is elutably trapped within the annealed polymeric material.

62. The intraluminal prosthesis of claim 61, wherein the pharmacological agent is selected from the group consisting of antineoplastics, antimitotics, antiinflammatories, antiplatelets, anticoagulants, antifibrins, antithrombins, antiproliferatives, antibiotics, antioxidants, immunosuppressives, antiallergic substances, and combinations thereof.

63. The intraluminal prosthesis of claim 54, wherein the polymeric material is heated to a temperature between the

glass transition temperature and the melting temperature of the polymeric material for a period of time sufficient to selectively increase or decrease stress in the intraluminal prosthesis.

64. The intraluminal prosthesis of claim 54, wherein the polymeric material is configured to erode at a first rate when deployed within a lumen of a subject body, and wherein the polymeric material is heated to a temperature between the glass transition temperature and the melting temperature of the polymeric material for a period of time sufficient to selectively modify the polymeric material such that it erodes at a second rate that is greater than the first rate when deployed within a lumen of a subject body.

65. The intraluminal prosthesis of claim 54, wherein the polymeric material is configured to erode at a first rate when deployed within a lumen of a subject body, and wherein the polymeric material is heated to a temperature between the glass transition temperature and the melting temperature of the polymeric material for a period of time sufficient to selectively modify the polymeric material such that it erodes at a third rate that is less than the first rate when deployed within a lumen of a subject body.

66. The intraluminal prosthesis of claim 54, wherein the polymeric material is heated in the presence of carbon dioxide.

67. The intraluminal prosthesis of claim 54, wherein the polymeric material is immersed in carbon dioxide prior to being heated.

68. The intraluminal prosthesis of claim 54, wherein the polymeric material is heated in the presence of a nucleating agent disposed on or within the polymeric material.

69. The intraluminal prosthesis of claim 54, wherein the intraluminal prosthesis is a stent.

70. The intraluminal prosthesis of claim 54, wherein the polymeric material is erodible.

71. The intraluminal prosthesis of claim 54, wherein the polymeric material is non-erodible.

72. The intraluminal prosthesis of claim 54, wherein the polymeric material is a coating on the tubular body.

73. The intraluminal prosthesis of claim 71, wherein the erodible polymeric material is selected from the group consisting of, surgical gut, silk, cotton, poly(hydroxybutyrate), polycarbonate, polyacrylate, polyanhydride, poly-(ortho esters), poly(phosphoesters), polyesters, polyamides, polyphosphazenes, poly(p-dioxane), poly(amino acid), polyglactin, erodable hydrogels, collagen, chitosan, poly-(lactic acid), poly(L-lactic acid), poly(D,L-lactic acid), poly(glycolic acid), poly(D-lactic-co-glycolic acid), poly(L-lactic-co-glycolic acid), poly(D,L-lactic-co-glycolic acid), poly(ε-caprolactone), poly(valerolactone), poly(hydroxy butyrate), poly(hydrovalerate), polydioxanone, poly(propylene fumarate), poly(ethyleneoxide)-poly(butylenetetraphthalate) poly(lactic acid-co-lysine), poly(lactic acid-co-trimethylene carbonate), poly(L-lactic acid) and poly(ε-caprolactone) copolymers.

74. The intraluminal prosthesis of claim 71, wherein the erodible polymeric material comprises a blend of polymeric material selected from the group consisting of, surgical gut, silk, cotton, poly(hydroxybutyrate), polycarbonate, polyacrylate, polyanhydride, poly(ortho esters), poly(phosphoesters), polyesters, polyamides, polyphosphazenes, poly(p-dioxane), poly(amino acid), polyglactin, erodable hydrogels, collagen, chitosan, poly(lactic acid), poly(L-lactic acid), poly(D,L-lactic acid), poly(glycolic acid), poly(D-lactic-co-glycolic acid), poly(L-lactic-co-glycolic acid), poly(D,L-lactic-co-glycolic acid), poly(ε-caprolactone), poly(valerolactone), poly(hydroxy butyrate), poly(hydrovalerate), polydioxanone, poly(propylene fumarate), poly(ethyleneoxide)-poly(butylenetetraphthalate), poly(lactic acid-co-lysine), poly(lactic acid-co-trimethylene carbonate), poly(L-lactic acid) and poly(ε-caprolactone) copolymers.

75. The intraluminal prosthesis of claim 54, wherein the polymeric material comprises oriented polymers.

76. The intraluminal prosthesis of claim 75, wherein the polymer orientation is uniaxial.

77. The intraluminal prosthesis of claim 75, wherein the polymer orientation is biaxial.

* * * * *

EXHIBIT D

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(54) **COATING FOR IMPLANTABLE DEVICES AND A METHOD OF FORMING THE SAME**

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(22) Filed: **Dec. 28, 2000**

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(63) Continuation-in-part of application No. 09/470,559, filed on Dec. 23, 1999. Continuation-in-part of application No. 09/715,510, filed on Nov. 17, 2000, which is a continuation-in-part of application No. 09/540,241, filed on Mar. 31, 2000.

Publication Classification

(51) **Int. Cl.**[7] **C08F 116/06**

(52) **U.S. Cl.** **525/60**

(57) **ABSTRACT**

Coatings for implantable devices or endoluminal prosthesis, such as stents, are provided, including a method of forming the coatings. The coatings can be used for the delivery of an active ingredient or a combination of active ingredients.

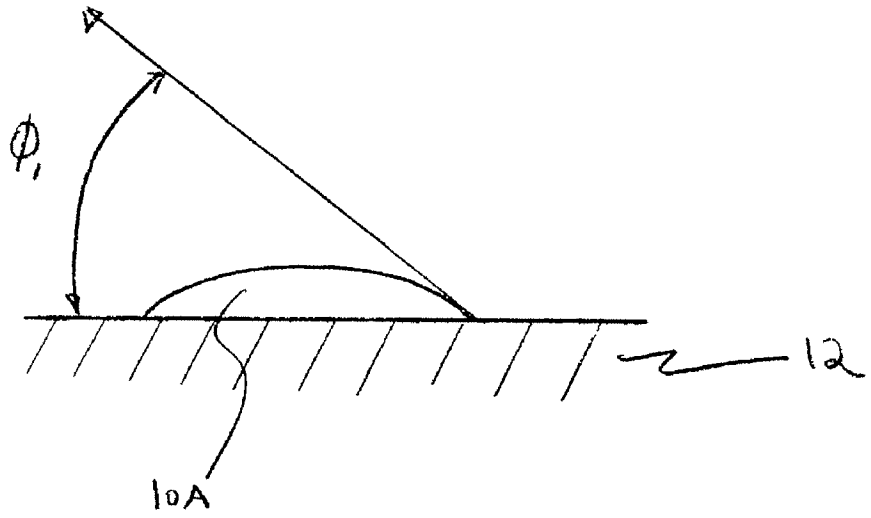

Figure 1A

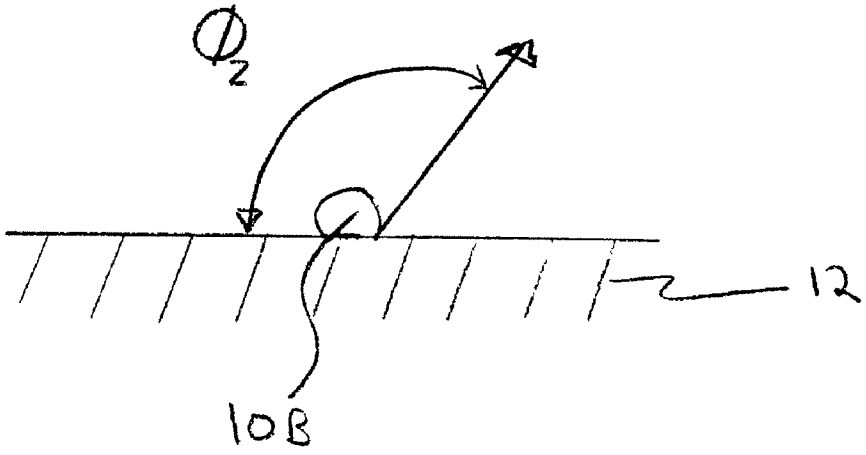

Figure 1B

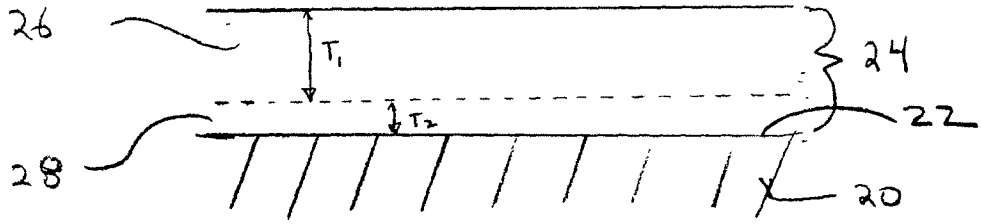

Figure 2A

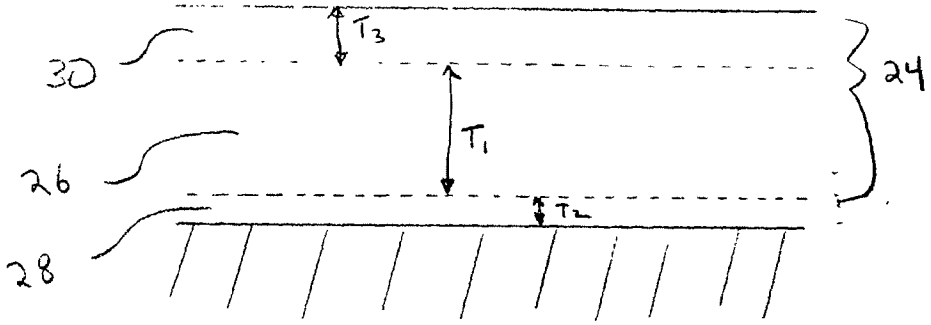

Figure 2B

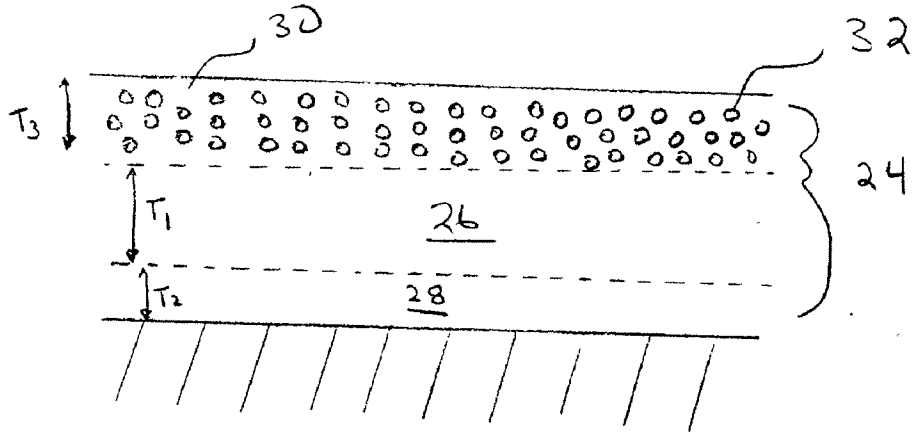

Figure 2C

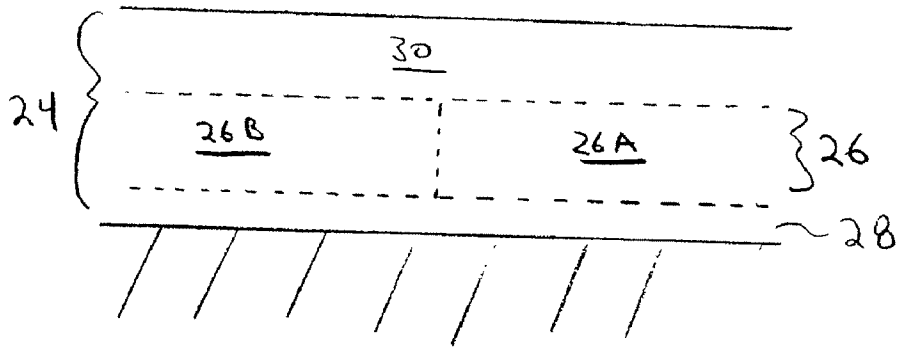

Figure 2D

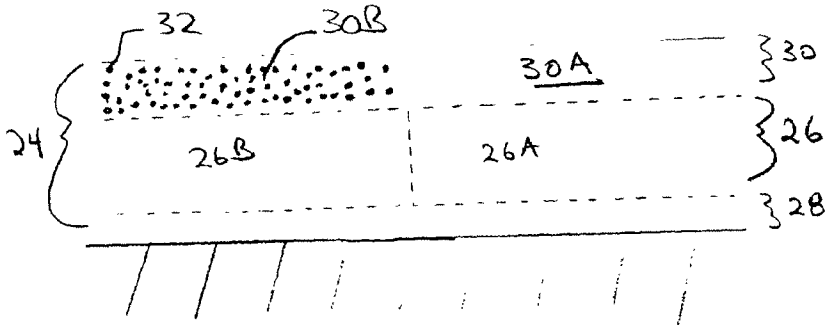

Figure 2E

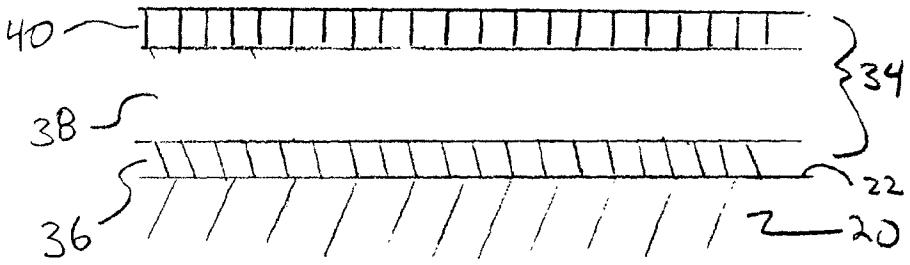

Figure 3A

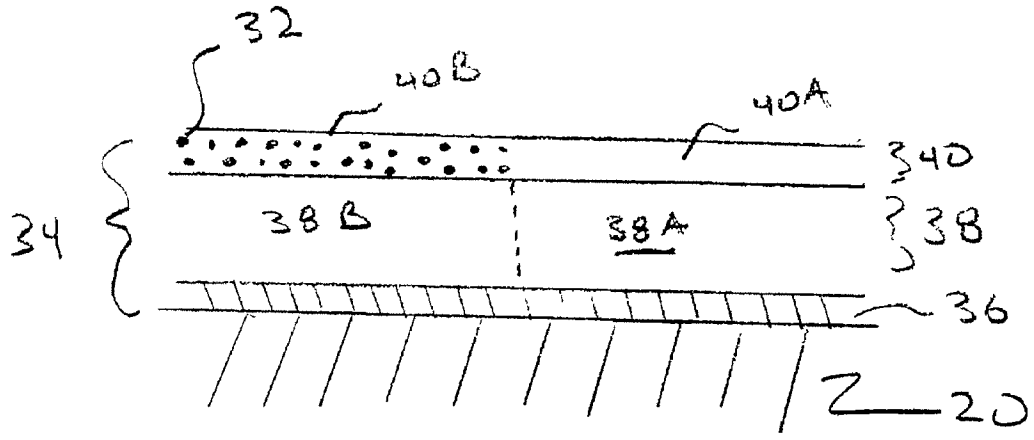

Figure 3B

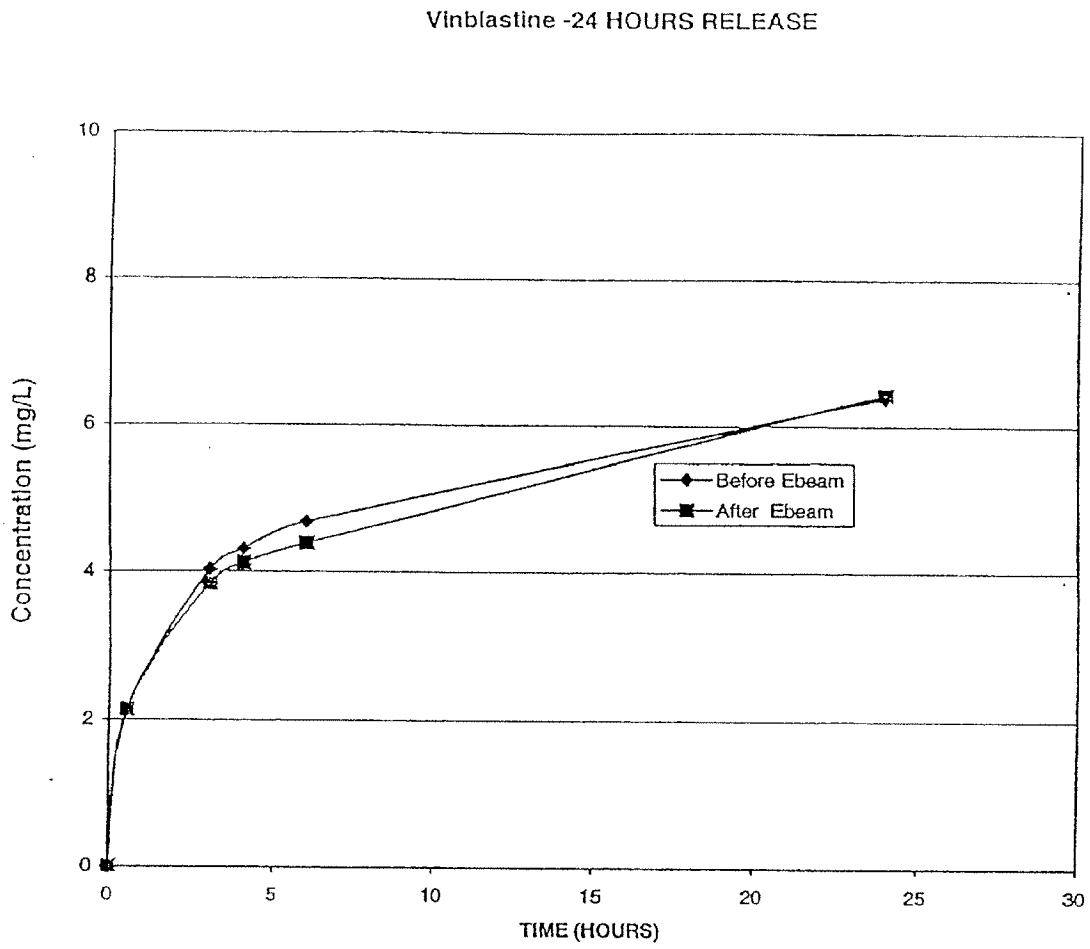
Vinblastine -24 HOURS RELEASE
Concentration (mg/L)
TIME (HOURS)
Before Ebeam
After Ebeam
0
2
4
6
8
10
0
5
10
15
20
25
30

Figure 4

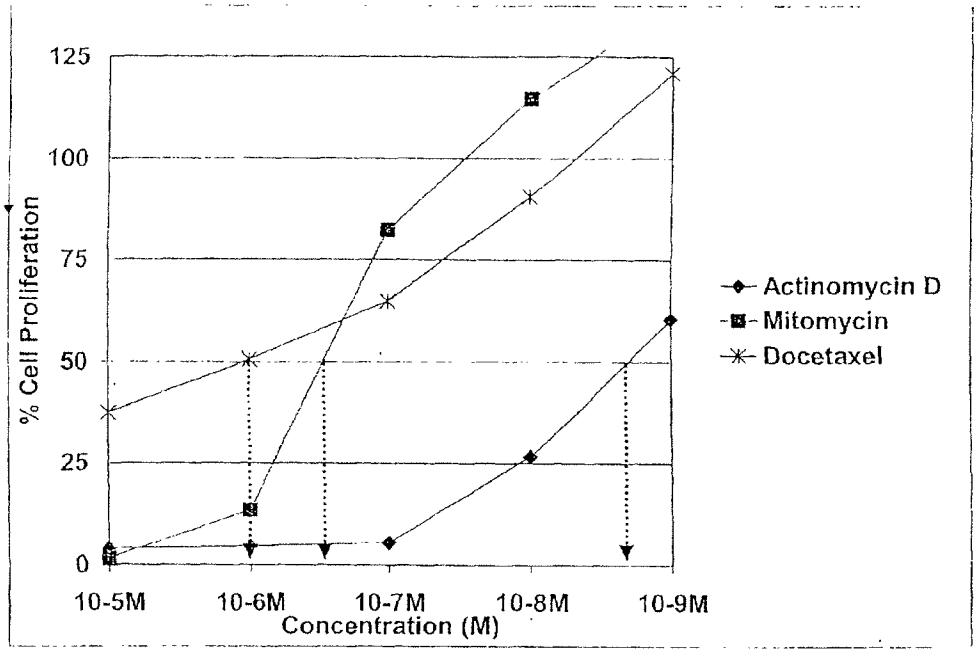
125
100
75
50
25
0
% Cell Proliferation
10-5M
10-6M
10-7M
10-8M
10-9M
Concentration (M)
Actinomycin D
Mitomycin
Docetaxel

Figure 5

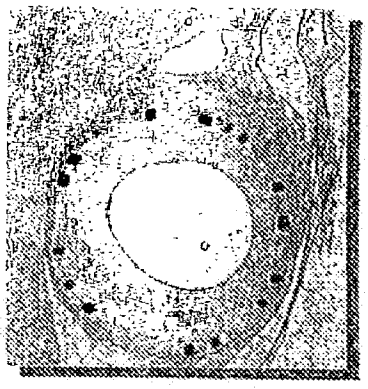

Figure 6A

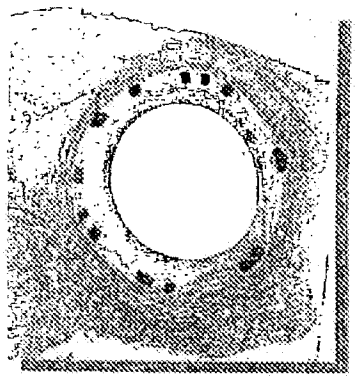

Figure 6B

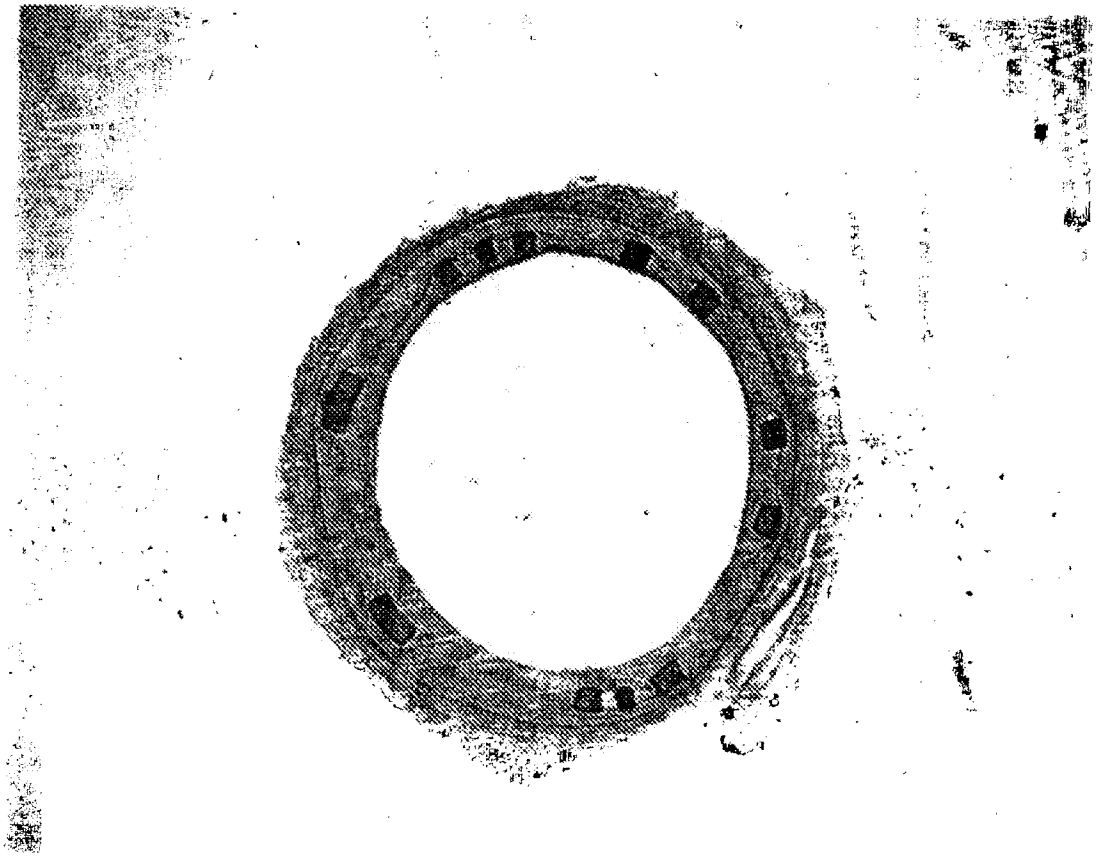

Figure 7A

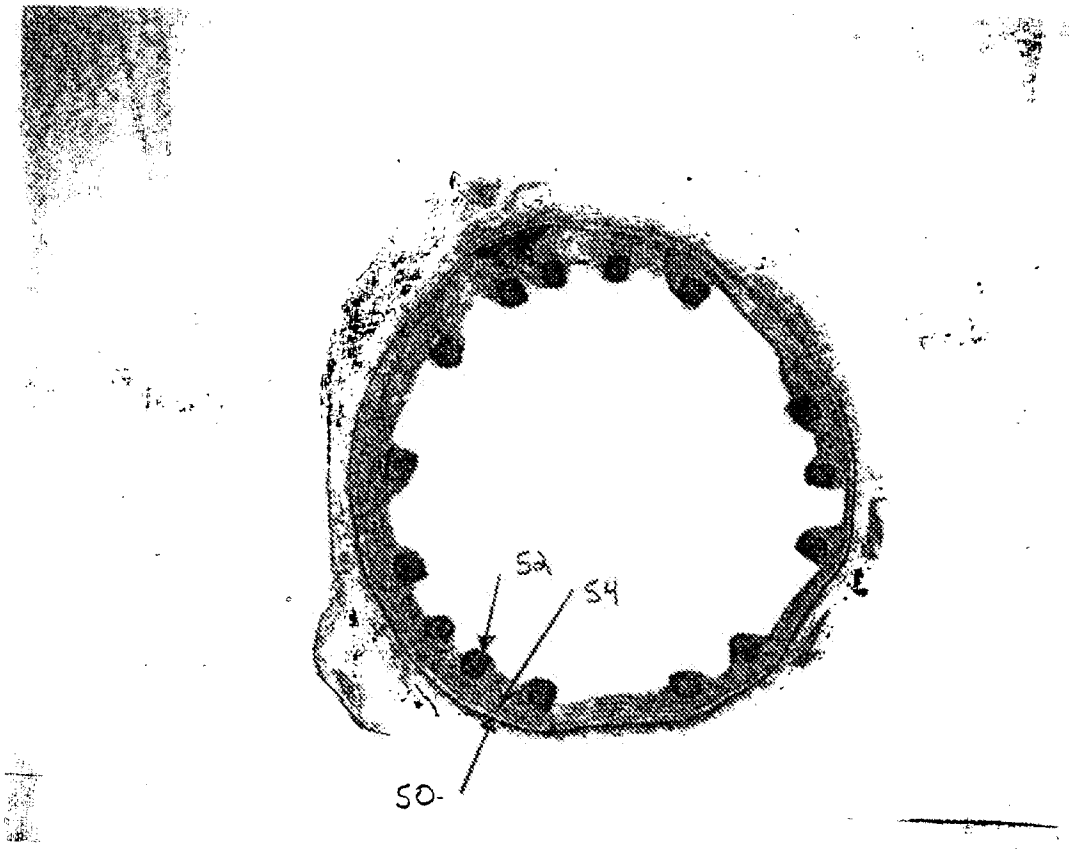

Figure 7B

COATING FOR IMPLANTABLE DEVICES AND A METHOD OF FORMING THE SAME

CROSS-REFERENCE

[0001] This is a continuation-in-part of U.S. patent application Ser. No. 09/470,559 filed on Dec. 23, 1999; this application is also a continuation-in-part of U.S. patent application serial number (unknown) filed on Nov. 17, 2000, which is a continuation-in-part of U.S. patent application Ser. No. 09/540,241 filed on Mar. 31, 2000.

BACKGROUND OF THE INVENTION

[0002] 1. Field of the Invention

[0003] The invention relates to coatings and methods of forming the coatings on implantable devices or endoluminal prostheses, such as stents.

[0004] 2. Description of the Background

[0005] Percutaneous transluminal coronary angioplasty (PTCA) is a procedure for treating heart disease. A catheter assembly having a balloon portion is introduced percutaneously into the cardiovascular system of a patient via the brachial or femoral artery. The catheter assembly is advanced through the coronary vasculature until the balloon portion is positioned across the occlusive lesion. Once in position across the lesion, the balloon is inflated to a predetermined size to radially press against the atherosclerotic plaque of the lesion for remodeling of the vessel wall. The balloon is then deflated to a smaller profile to allow the catheter to be withdrawn from the patient's vasculature.

[0006] A problem associated with the above procedure includes formation of intimal flaps or torn arterial linings which can collapse and occlude the conduit after the balloon is deflated. Vasospasms and recoil of the vessel wall also threaten vessel closure. Moreover, thrombosis and restenosis of the artery may develop over several months after the procedure, which may require another angioplasty procedure or a surgical by-pass operation. To reduce the partial or total occlusion of the artery by the collapse of arterial lining, and to reduce the chance of the development of thrombosis and restenosis, an expandable, intraluminal prosthesis, one example of which includes a stent, is implanted in the lumen to maintain the vascular patency.

[0007] Stents are used not only as a mechanical intervention but also as a vehicle for providing biological therapy. As a mechanical intervention, stents act as scaffoldings, functioning to physically hold open and, if desired, to expand the wall of the passageway. Typically stents are capable of being compressed, so that they can be inserted through small cavities via catheters, and then expanded to a larger diameter once they are at the desired location. Examples in the patent literature disclosing stents which have been successfully applied in PTCA procedures include stents illustrated in U.S. Pat. No. 4,733,665 issued to Palmaz, U.S. Pat. No. 4,800,882 issued to Gianturco, and U.S. Pat. No. 4,886,062 issued to Wiktor. Mechanical intervention via stents has reduced the rate of restenosis as compared to balloon angioplasty; but restenosis is still a significant clinical problem with rates ranging from 20-40%. When restenosis does occur in the stented segment, its treatment can be challenging, as clinical options are more limited as compared to lesions that were treated solely with a balloon.

[0008] Biological therapy can be achieved by medicating the stents. Medicated stents provide for the local administration of a therapeutic substance at the diseased site. In order to provide an efficacious concentration to the treated site, systemic administration of such medication often produces adverse or toxic side effects for the patient. Local delivery is a preferred method of treatment in that smaller total levels of medication are administered in comparison to systemic dosages, but are concentrated at a specific site. Local delivery thus produces fewer side effects and achieves more favorable results.

[0009] One proposed method for medicating stents disclosed seeding the stents with endothelial cells (Dichek, D. A. et al. Seeding of Intravascular Stents With Genetically Engineered Endothelial Cells; Circulation 1989; 80: 1347-1353). Briefly, endothelial cells were seeded onto stainless steel stents and grown until the stents were covered. The cells were therefore able to be delivered to the vascular wall where they provided therapeutic proteins. Another proposed method of providing a therapeutic substance to the vascular wall included use of a heparin-coated metallic stent, whereby a heparin coating was ionically or covalently bonded to the stent. Significant disadvantages associated with the aforementioned method includes significant loss of the therapeutic substance from the body of the stent during delivery and expansion of the stent, an absolute lack of control of the release rate of the proteins from the stent, and the inherent limitation as to the type of therapeutic substance that can be used.

[0010] Another proposed method involved the use of a polymeric carrier coated onto the surface of a stent, as disclosed in U.S. Pat. No. 5,464,650 issued to Berg et al. Berg disclosed applying to a stent body a solution which included a specified solvent, a specified polymer dissolved in the solvent, and a therapeutic substance dispersed in the blend. The solvent was allowed to evaporate, leaving on the stent surface a coating of the polymer and the therapeutic substance impregnated in the polymer. Among the specified, suitable choices of polymers listed by Berg, empirical results were specifically provided for poly(caprolactone) and poly(L-lactic acid). The preferred choice of mutually compatible solvents included acetone or chloroform. As indicated in Berg, stents where immersed in the solution 12 to 15 times or sprayed 20 times. The evaporation of the solvent provided a white coating. A white coloration is generally indicative of a brittle coating. A brittle coating is an undesirable characteristic, since portions of the coating typically become detached during stent expansion. Detachment of the coating causes the quality of the therapeutic substance to fall below a threshold level sufficient for the effective treatment of a patient.

[0011] It is desirable to improve the adhesion or retention of the polymeric coating to the surface of a prosthesis, e.g., stent. It is also desirable to be able to increase the quantity of the therapeutic substance carried by the polymeric layer without perturbing the mechanical properties of the coating, such as inadequate coating adhesion, or significantly increasing the thickness of the coating.

[0012] It is additionally desirable to provide an improved polymeric coating that is susceptible to delivery and expansion with a prosthesis without significant detachment from the surface of the prosthesis. An improved polymeric coat-

ing is also needed which allows for a significant control of the release of the therapeutic substance.

[0013] It may also be advantageous to maintain the concentration of the therapeutic substance at a therapeutically acceptable level for a prolonged duration of time. Depending on the physiological mechanism targeted, the therapeutic substance may be required to be released at the target site for an extended duration of time. Accordingly, it is desirable to provide a coating which can maintain the residence time of a substance at a therapeutically useful concentration for an effective duration of time.

SUMMARY OF THE INVENTION

[0014] In accordance with one aspect of the present invention, a prosthesis is provided, such as a balloon-expandable stent or a self-expandable stent, which includes a coating having a reservoir region carrying an active ingredient, e.g., actinomycin D or taxol. A primer region, free from any active ingredients, can be disposed between the reservoir region and the surface of the prosthesis. The primer can act as an intermediary tie layer between the surface of the prosthesis and the reservoir region. The primer and reservoir regions can be made form the same polymeric material or different polymeric materials. The prosthesis can additionally include a barrier region disposed on a selected portion of the reservoir region for reducing the rate at which the active ingredient is released. In one embodiment, the barrier layer contains inorganic particles. Examples of suitable polymeric materials for the primer layer include polyisocyanates, unsaturated polymers, amine content polymers, acrylates, polymers containing a high content of hydrogen bonding groups, and inorganic polymers. Biocompatible polymers can be used not only for the primer region, but also for the reservoir region. One examples of a biocompatible polymer includes ethylene vinyl alcohol copolymer.

[0015] In accordance with another aspect of the present invention, a method is provided for forming a coating for an implantable device comprising forming a primer on at lease a selected portion of a surface of the implantable device and forming a reservoir region containing an active ingredient on at least a selected portion of the primer. The primer can provide an adhesive tie layer between the surface of the implantable device and the reservoir region. In one embodiment, the method can additionally include forming a barrier layer on at lease a selected portion of the reservoir region for reducing the rate at which the active ingredient is released from the reservoir region.

[0016] In one embodiment, the act of forming the primer comprises applying a composition to a selected portion of the surface of the implantable device wherein the composition includes a thermoplastic polymer added to a solvent, and heating the composition applied to the implantable device to a temperature greater than about the glass transition temperature and less than about the melting temperature of the polymer.

[0017] In accordance with another embodiment, the act of forming the primer comprises applying a composition to a selected portion of the surface of the implantable device, wherein the composition comprises an inorganic polymer added to a solvent, and significantly removing the solvent to form the primer.

[0018] In accordance with another embodiment, the act of forming the primer comprises applying a composition to a selected portion of the surface of the implantable device, wherein the composition comprises a polymer added to a solvent, and heating the composition applied to the selected portion of the surface of the implantable device to a temperature above the glass transition temperature of the polymer.

[0019] In accordance with another embodiment, the act of forming the primer comprises applying a composition to a selected portion of the surface of the implantable device, wherein the composition comprises a prepolymer and an initiator, e.g., a free radical or UV initiator. The composition is then exposed to a condition such as UV radiation or heat to polymerize the prepolymer.

[0020] In accordance with another aspect of the present invention, a coating for a stent is provided containing a first active ingredient and a second active ingredient, wherein the rate of release of the first active ingredient is slower than the rate of release of the second active ingredient. The coating can be made from a polymeric material such as an ethylene vinyl alcohol copolymer. The coating can include a first region containing the first and second active ingredients, and a second region, free from any active ingredients, located between the first region and the surface of the stent. The second region increases the ability of the coating to be retained by the stent.

BRIEF DESCRIPTION OF THE FIGURE

[0021] **FIG. 1A** illustrates a fluid on a solid substrate having a contact angle ϕ_1;

[0022] **FIG. 1B** illustrates a fluid on a solid substrate having a contact angle ϕ_2;

[0023] FIGS. **2A-2E** illustrate a coating in accordance with some of the embodiment of the present invention;

[0024] **FIGS. 3A and 3B** illustrate a coating having different layers;

[0025] **FIG. 4** graphically illustrates elution profiles for stents with a coating of ethylene vinyl alcohol copolymer impregnated with vinblastine made according to Example 4;

[0026] **FIG. 5** graphically illustrates in vitro experimental data, in accordance with Example 15, showing affects of actinomycin D, mitomycin, and docetaxel on smooth muscle cell proliferation;

[0027] **FIG. 6A** is a picture of a histology slide of a coronary vessel from the control group in accordance with Example 16;

[0028] **FIG. 6B** is a picture of a histology slide of a coronary vessel from the actinomycin D group in accordance with Example 16

[0029] **FIG. 7A** is a picture of a histology slide of a coronary vessel from the control group in accordance with Example 26; and

[0030] **FIG. 7B** is a picture of a histology slide of a coronary vessel from the actinomycin D group in accordance with Example 26.

DETAILED DESCRIPTION OF THE EMBODIMENTS

Composition for Forming The Primer Layer

[0031] The embodiments of the composition for a primer layer are prepared by conventional methods wherein all

components are combined, then blended. More particularly, in accordance to one embodiment, a predetermined amount of a polymer or a prepolymer is added to a predetermined amount of a solvent or a combination of solvents. The mixture can be prepared in ambient pressure and under anhydrous atmosphere. If necessary, a free radical or UV initiator can be added to the composition for initiating the curing or cross-linking of the prepolymer. Heating and stirring and/or mixing can be employed to effect dissolution of the polymer into the solvent.

[0032] "Polymer,""poly," and "polymeric" are defined as compounds that are the product of a polymerization reaction and are inclusive of homopolymers, copolymers, terpolymers etc., including random, alternating, block, and graft variations thereof. The polymers should have a high capacity of adherence to the surface of an implantable device, such as a metallic surface of a stent. Stainless steel, such as 316L, is a commonly used material for the manufacturing of a stent. Stainless steel includes a chromium oxide surface layer which makes the stent corrosion resistant and confers, in large part, biocompatibility properties to the stent. The chromium oxide layer presents oxide, anionic groups, and hydroxyl moieties, which are polar. Consequently, polymeric materials with polar substituents and cationic groups can adhere to the surface. Representative examples of suitable polymeric material include polyisocyanates, unsaturated polymers, high amine content polymers, acrylates, polymers with high content of hydrogen bonding groups, silane coupling agents, titanates and zirconates.

[0033] Representative examples of polyisocyanates include triisocyanurate, alphatic polyisocyanate resins based on hexamethylene diisocyanate, aromatic polyisocyanate prepolymers based on diphenylmethane diisocyanate, polyisocyanate polyether polyurethanes based on diphenylmethane diisocyanate, polymeric isocyanates based on toluene diisocyanate, polymethylene polyphenyl isocyanate, and polyester polyurethanes.

[0034] Representative examples of unsaturated polymers include polyester diacrylates, polycaprolactone diacrylates, polyester diacrylates, polytetramethylene glycol diacrylate, polyacrylates with at least two acrylate groups, polyacrylated polyurethanes, and triacrylates. With the use of unsaturated prepolymers a free radical or UV initiator can be added to the composition for the thermal or UV curing or cross-linking process. For thermal curing, examples of free radicals initiators are benzoyl peroxide; bis(2,4-dichlorobenzoyl) peroxide; dicumyl peroxide; 2,5-bis(tert-butyl peroxy)-2,5-dimethyl hexane; ammonium persulfate, and 2,2'-azobisisobutyronitrile. As is understood by one of ordinary skill in the art, each initiator requires a different temperature to induce decomposition. For UV curing, examples of initiators include 2,2-dimethoxy-2-phenylacetophenone; 1-hydroxycyclohexyl phenyl ketone; benzoin ethyl ether; and benzophenone. These initators can be activated by illumination with a medium pressure Hg bulb that contains wavelengths between 250 and 350 nm.

[0035] Representative examples of high amine content polymers include polyethyleneamine, polyallylamine, and polylysine.

[0036] Representative examples of acrylates include copolymers of ethyl acrylate, methyl acrylate, butyl methacrylate, methacrylic acid, acrylic acid, and cyanoacrylates.

[0037] Representative examples of high content of hydrogen bonding group polymers include polyethylene-co-polyvinyl alcohol, epoxy polymers based on the diglycidylether of bisphenol A with amine crosslinking agents, epoxy polymers cured by polyols and lewis acid catalysts, epoxy phenolics, epoxy-polysulfides, ethylene vinyl acetate, melamine formaldehydes, polyvinylalcohol-co-vinyl acetate polymers, resorcinol-formaldehydes, urea-formaldehydes, polyvinylbutyral, polyvinylacetate, alkyd polyester resins, acrylic acid modified ethylene vinyl acetate polymers, methacrylic acid modified ethylene vinyl acetate polymers, acrylic acid modified ethylene acrylate polymers, methacrylic acid modified ethylene acrylate polymers, anhydride modified ethylene acrylate coppolymers, and anhydride modified ethylene vinyl acetate polymers.

[0038] Representative examples of silane coupling agents include 3-aminopropyltriethoxysilane and (3-glydidoxypropyl)methyldiethoxysilane.

[0039] Representative examples of titanates include tetra-iso-propyl titanate and tetra-n-butyl titanate.

[0040] Representative examples of zirconates include n-propyl zirconate and n-butyl zirconate.

[0041] Biocompatible polymers can also be used for the primer material. Examples of biocompatible primers include poly(hydroxyvalerate), poly(L-lactic acid), polycaprolactone, poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), polydioxanone, polyorthoesters, polyanhydrides, poly(glycolic acid), poly(D,L-lactic acid), poly(glycolic acid-co-trimethylene carbonate), polyphosphoesters, polyphosphoester urethanes, poly(amino acids), cyanoacrylates, poly(trimethylene carbonates), poly(iminocarbonate), copoly(ether-esters) (e.g. PEO/PLA), polyalkylene oxalates, polyphosphazenes and biomolecules such as fibrin, fibrinogen, cellulose, starch, collagen and hyaluronic acid. Also, polyurethanes, silicones, and polyesters could be used and other polymers could also be used if they can be dissolved and cured or polymerized on the stent such as polyolefins, polyisobutylene and ethylene-alphaolefin copolymers; acrylic polymers and copolymers, vinyl halide polymers and copolymers, such as polyvinyl chloride; polyvinyl ethers, such as polyvinyl methyl ether; polyvinylidene halides, such as polyvinylidene fluoride and polyvinylidene chloride; polyacrylonitrile; polyvinyl ketones; polyvinyl aromatics, such as polystyrene; polyvinyl esters, such as polyvinyl acetate; copolymers of vinyl monomers with each other and olefins, such as ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins, and ethylene-vinyl acetate copolymers; polyamides, such as Nylon 66 and polycaprolactam; alkyd resins; polycarbonates; polyoxymethylenes; polyimides; polyethers; epoxy resins; rayon; rayon-triacetate; cellulose, cellulose acetate, cellulose butyrate; cellulose acetate butyrate; cellophane; cellulose nitrate; cellulose propionate; cellulose ethers; and carboxymethyl cellulose.

[0042] Ethylene vinyl alcohol is functionally a very suitable choice of polymer. Ethylene vinyl alcohol copolymer, commonly known by the generic name EVOH or by the trade name EVOH, refers to copolymers comprising residues of both ethylene and vinyl alcohol monomers. One of ordinary skill in the art understands that ethylene vinyl alcohol copolymer may also be a terpolymer so as to include small amounts of additional monomers, for example less

than about five (5) mole percentage of styrenes, propylene, or other suitable monomers. In a useful embodiment, the copolymer comprises a mole percent of ethylene of from about 27% to about 47%. Typically, 44 mole percent ethylene is suitable. Ethylene vinyl alcohol copolymers are available commercially from companies such as Aldrich Chemical Company, Milwaukee, Wis., or EVOH Company of America, Lisle, Ill., or can be prepared by conventional polymerization procedures that are well known to one of ordinary skill in the art. The copolymer possesses good adhesive qualities to the surface of a stent, particularly stainless steel surfaces, and has illustrated the ability to expand with a stent without any significant detachment of the copolymer from the surface of the stent.

[0043] The solvent should be mutually compatible with the polymer and should be capable of placing the polymer into solution at the concentration desired in the solution. Useful solvents should also be able to expand the chains of the polymer for maximum interaction with the surface of the device, such as a metallic surface of a stent. Examples of solvent can include, but are not limited to, dimethylsulfoxide (DMSO), chloroform, acetone, water (buffered saline), xylene, acetone, methanol, ethanol, 1-propanol, tetrahydrofuran, 1-butanone, dimethylformamide, dimethylacetamide, cyclohexanone, ethyl acetate, methylethylketone, propylene glycol monomethylether, isopropanol, N-methyl pyrrolidinone, toluene and mixtures thereof.

[0044] By way of example, and not limitation, the polymer can comprise from about 0.1% to about 35%, more narrowly about 2% to about 20% by weight of the total weight of the composition, and the solvent can comprise from about 65% to about 99.9%, more narrowly about 80% to about 98% by weight of the total weight of the composition. A specific weight ratio is dependent on factors such as the material from which the implantable device is made and the geometrical structure of the device.

[0045] In accordance with another embodiment, a fluid can be added to the composition to enhance the wetting of the composition for a more uniform coating application. To enhance the wetting of the composition, a suitable fluid typically has a high capillary permeation. Capillary permeation or wetting is the movement of a fluid on a solid substrate driven by interfacial energetics. Capillary permeation is quantitated by a contact angle, defined as an angle at the tangent of a droplet in a fluid phase that has taken an equilibrium shape on a solid surface. A low contact angle means a higher wetting liquid. A suitably high capillary permeation corresponds to a contact angle less than about 90°. **FIG. 1A** illustrates a fluid droplet **10A** on a solid substrate **12**, for example a stainless steel surface. Fluid droplet **10A** has a high capillary permeation that corresponds to a contact angle ϕ_1, which is less than about 90°. In contrast, **FIG. 1B** illustrates a fluid droplet **10B** on solid substrate **12**, having a low capillary permeation that corresponds to a contact angle ϕ_2, which is greater than about 90°. The wetting fluid, typically, should have a viscosity not greater than about 50 centipoise, narrowly about 0.3 to about 5 centipoise, more narrowly about 0.4 to about 2.5 centipoise. The wetting fluid, accordingly, when added to the composition, reduces the viscosity of composition.

[0046] The wetting fluid should be mutually compatible with the polymer and the solvent and should not precipitate the polymer. The wetting fluid can also act as the solvent. Useful examples of the wetting fluid include, but are not limited to, tetrahydrofuran (THF), dimethylformamide (DMF), 1-butanol, n-butyl acetate, dimethyl acetamide (DMAC), and mixtures and combinations thereof. By way of example and not limitation, the polymer can comprise from about 0. 1% to about 35%, more narrowly from about 2% to about 20% by weight of the total weight of the composition; the solvent can comprise from about 19.9% to about 98.9%, more narrowly from about 58% to about 84% by weight of the total weight of the composition; the wetting fluid can comprise from about 1% to about 80%, more narrowly from about 5% to about 40% by weight of the total weight of the composition. The specific weight ratio of the wetting fluid depends on the type of wetting fluid employed and type of and the weight ratio of the polymer and the solvent. More particularly, tetrahydrofuran used as the wetting fluid can comprise, for example, from about 1% to about 44%, more narrowly about 21% by weight of the total weight of the solution. Dimethylformamide used as the wetting fluid can comprise, for example, from about 1% to about 80%, more narrowly about 8% by weight of the total weight of the solution. 1-butanol used as the wetting fluid can comprise, for example, from about 1% to about 33%, more narrowly about 9% by weight of the total weight of the solution. N-butyl acetate used as the wetting fluid can comprise, for example, from about 1% to about 34%, more narrowly about 14% by weight of the total weight of the solution. Dimethyl acetamide used as the wetting fluid can comprise, for example, from about 1% to about 40%, more narrowly about 20% by weight of the total weight of the solution.

[0047] The presence of an active ingredient in a polymeric matrix typically interferes with the ability of the matrix to adhere effectively to the surface of the device. An increase in the quantity of the active ingredient reduces the effectiveness of the adhesion. High drug loadings of, for example, 10-40% by weight in the coating significantly hinder the retention of the coating on the surface of the device. The primer layer serves as a functionally useful intermediary layer between the surface of the device and an active ingredient-containing or reservoir coating. The primer layer provides for an adhesive tie between the reservoir coating and the device—which, in effect, would also allow for the quantity of the active ingredient in the reservoir coating to be increased without compromising the ability of the reservoir coating to be effectively contained on the device during delivery and, if applicable, expansion of the device. Ethylene vinyl alcohol copolymer adheres well to metallic surfaces, particularly devices made from stainless steel. The copolymer has illustrated good elastic qualities, which allow the copolymer to be delivered and, if applicable, expanded with the device without any significant detachment of the copolymer form the surface of the device.

[0048] Table 1 illustrates some examples of suitable combinations for the primer composition:

TABLE 1

Polymer	Solvent	Wetting Fluid	Initiators
EVOH	DMSO	—	—
EVOH	DMSO	THF	—
polyester polyurethanes	dimethylformamide	—	—
polyester polyurethanes	dimethylformamide	DMAC	—
polycaprolactone	chloroform	n-butyl acetate	
polyacrylate polyurethane	ethyl acetate	—	benzophenone
polyacrylated polyurethane	ethyl acetate	—	1-hydroxycyclohexyl phenyl ketone
polyethyleneamine	H_2O	—	—
methacrylic acid copolymer	THF	—	—
ethylene vinylacetate (e.g., 40% vinyl acetate content)	methylethylketone	—	—
aminopropyltriethoxysilane	ethanol/water 95/5 blend (w/w)	—	—
(3-glydidoxypropyl) methyldiethoxysilane	toluene	—	—
tetra-iso-propyl titanate (e.g., 0.25% w/w in isopropanol)	isopropanol	—	—
tetra-n-butyl titanate (e.g., 0.1–5% w/w in ethyl acetate)	ethyl acetate	—	—

[0049] Composition for Forming The Active Ingredient Layer

[0050] The embodiments of the composition for an active ingredient-containing or reservoir layer are prepared by conventional methods wherein all components are combined, then blended. More particularly, in accordance to one embodiment, a predetermined amount of a polymeric compound is added to a predetermined amount of a mutually compatible solvent or combination of solvents. The polymeric compound can be added at ambient pressure and under anhydrous atmosphere. If necessary, gentle heating and stirring and/or mixing can be employed to effect dissolution of the polymer into the solvent, for example 12 hours in a water bath at about 60° C.

[0051] The polymer chosen must be a polymer that is biocompatible and minimizes irritation to the vessel wall when the device is implanted. The polymer may be either a biostable or a bioabsorbable polymer. Bioabsorbable polymers that could be used include poly(hydroxyvalerate), poly(L-lactic acid), polycaprolactone, poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), polydioxanone, polyorthoesters, polyanhydrides, poly(glycolic acid), poly(D,L-lactic acid), poly(glycolic acid-co-trimethylene carbonate), polyphosphoesters, polyphosphoester urethanes, poly(amino acids), cyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), copoly(ether-esters) (e.g. PEO/PLA), polyalkylene oxalates, polyphosphazenes and biomolecules such as fibrin, fibrinogen, cellulose, starch, collagen and hyaluronic acid. Also, biostable polymers with a relatively low chronic tissue response such as polyurethanes, silicones, and polyesters could be used and other polymers could also be used if they can be dissolved and cured or polymerized on the stent such as polyolefins, polyisobutylene and ethylene-alphaolefin copolymers; acrylic polymers and copolymers, vinyl halide polymers and copolymers, such as polyvinyl chloride; polyvinyl ethers, such as polyvinyl methyl ether; polyvinylidene halides, such as polyvinylidene fluoride and polyvinylidene chloride; polyacrylonitrile; polyvinyl ketones; polyvinyl aromatics, such as polystyrene; polyvinyl esters, such as polyvinyl acetate; copolymers of vinyl monomers with each other and olefins, such as ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins, and ethylene-vinyl acetate copolymers; polyamides, such as Nylon 66 and polycaprolactam; alkyd resins; polycarbonates; polyoxymethylenes; polyimides; polyethers; epoxy resins; rayon; rayon-triacetate; cellulose, cellulose acetate, cellulose butyrate; cellulose acetate butyrate; cellophane; cellulose nitrate; cellulose propionate; cellulose ethers; and carboxymethyl cellulose.

[0052] Ethylene vinyl alcohol is functionally a very suitable choice of polymer. The copolymer allows for good control capabilities over the release rate of the active ingredient. As a general rule, an increase in the amount of the ethylene comonomer content decreases the rate that the active ingredient is released from the copolymer matrix. The release rate of the active ingredient typically decreases as the hydrophilicity of the copolymer decreases. An increase in the amount of the ethylene comonomer content increases the overall hydrophobicity of the copolymer, especially as the content of vinyl alcohol is concomitantly reduced. It is also known that the release rate and the cumulative amount of the active ingredient that is released is directly proportional to the total initial content of the ingredient in the copolymer matrix. Accordingly, a wide spectrum of release rates can be achieved by modifying the ethylene comonomer content and the initial amount of the active ingredient.

[0053] The choice of polymer for the reservoir layer can be the same as or different from the selected polymer for the primer layer. The use of the same polymer significantly reduces or eliminates any interfacial incompatibilities, such as lack of an adhesive tie or bond, which may exist with the employment of two different polymeric layers. In effect, it can be said that the use of the same polymeric material for the primer layer and the reservoir layer results in the formation of a single-layered coating.

[0054] The solvent should be capable of placing the polymer into solution at the concentration desired in the solution. Examples of solvent can include, but are not limited to, DMSO, chloroform, acetone, water (buffered saline), xylene, acetone, methanol, ethanol, 1-propanol, tetrahydrofuran, 1-butanone, dimethylformamide, dimethylacetamide, cyclohexanone, and N-methyl pyrrolidinone. With the use of low ethylene content, e.g., 29 mol %, ethylene vinyl alcohol copolymer, a suitable choice of solvent is iso-propylalcohol (IPA) admixed with water.

[0055] Sufficient amounts of an active ingredient are dispersed in the blended composition of the polymer and the solvent. The active ingredient should be in true solution or saturated in the blended composition. If the active ingredient is not completely soluble in the composition, operations including mixing, stirring, and/or agitation can be employed to effect homogeneity of the residues. The active ingredient may be added so that the dispersion is in fine particles. The mixing of the active ingredient can be conducted in an anhydrous atmosphere, at ambient pressure, and at room temperature such that supersaturating the active ingredient is not desired.

[0056] The active ingredient should inhibit the activity of vascular smooth muscle cells. More specifically, the active ingredient is aimed at inhibiting abnormal or inappropriate migration and/or proliferation of smooth muscle cells.

[0057] "Smooth muscle cells" include those cells derived from the medial and adventitial layers of the vessel which proliferate in intimal hyperplastic vascular sites following vascular trauma or injury. Under light microscopic examination, characteristics of smooth muscle cells include a histological morphology of a spindle shape with an oblong nucleus located centrally in the cell with nucleoli present and myofibrils in the sarcoplasm. Under electron microscopic examination, smooth muscle cells have long slender mitochondria in the juxtanuclear sarcoplasm, a few tubular elements of granular endoplasmic reticulum, and numerous clusters of free ribosomes. A small Golgi complex may also be located near one pole of the nucleus.

[0058] "Migration" of smooth muscle cells means movement of these cells in vivo from the medial layers of a vessel into the intima, such as may also be studied in vitro by following the motion of a cell from one location to another, e.g., using time-lapse cinematography or a video recorder and manual counting of smooth muscle cell migration out of a defined area in the tissue culture over time.

[0059] "Proliferation" of smooth muscle cells means increase in cell number.

[0060] "Abnormal" or "inappropriate" proliferation means division, growth or migration of cells occurring more rapidly or to a significantly greater extent than typically occurs in a normally functioning cell of the same type, i.e., hyper-proliferation.

[0061] "Inhibiting" cellular activity means reducing, delaying or eliminating smooth muscle cell hyperplasia, restenosis, and vascular occlusions, particularly following biologically or mechanically mediated vascular injury or trauma or under conditions that would predispose a mammal to suffer such a vascular injury or trauma. As used herein, the term "reducing" means decreasing the intimal thickening that results from stimulation of smooth muscle cell proliferation. "Delaying" means retarding the progression of the hyper-proliferative vascular disease or delaying the time until onset of visible intimal hyperplasia, as observed, for example, by histological or angiographic examination. "Elimination" of restenosis following vascular trauma or injury means completely "reducing" and/or completely "delaying" intimal hyperplasia in a patient to an extent which makes it no longer necessary to surgically intervene, i.e., to re-establish a suitable blood flow through the vessel by, for example, repeat angioplasty, atherectomy, or coronary artery bypass surgery. The effects of reducing, delaying, or eliminating restenosis may be determined by methods known to one of ordinary skill in the art, including, but not limited to, angiography, intravascular ultrasound, fluoroscopic imaging, fiber optic visualization, optical coherence tomography, intravascular MRI, or biopsy and histology. Biologically mediated vascular injury includes, but is not limited to, injury caused by or attributed to autoimmune disorders, alloimmune related disorders, infectious disorders including endotoxins and herpes viruses such as cytomegalovirus, metabolic disorders such as atherosclerosis, and vascular injury resulting from hypothermia and irradiation. Mechanically mediated vascular injury includes, but is not limited to, vascular injury caused by catheterization procedures or vascular scraping procedures such as percutaneous transluminal coronary angioplasty, vascular surgery, stent placement, transplantation surgery, laser treatment, and other invasive procedures which disrupted the integrity of the vascular intima or endothelium. The active ingredient of the invention is not restricted in use for therapy following vascular injury or trauma; rather, the usefulness of the active ingredient will also be determined by the ingredient's ability to inhibit cellular activity of smooth muscle cells or inhibit the development of restenosis.

[0062] The active ingredient also includes any substance capable of exerting a therapeutic or prophylactic effect in the practice of the present invention as well as having positive pharmacological effects on the expression of the extracellular matrix. The active ingredient can also be for enhancing wound healing in a vascular site and improving the structural and elastic properties of the vascular site. Examples of such active ingredients include antiproliferative substances as well as antineoplastic, antiinflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antimitotic, antibiotic, antioxidant, and combinations thereof. A suitable example of an antiproliferative substance includes actinomycin D, or derivatives and analogs thereof (manufactured by Sigma-Aldrich 1001 West Saint Paul Avenue, Milwaukee, Wis. 53233; or COSMEGEN available from Merck). Synonyms of actinomycin D include dactinomycin, actinomycin IV, actinomycin I_1, actinomycin X_1, and actinomycin C_1. Examples of suitable antineoplastics include paclitaxel and docetaxel. Examples of suitable antiplatelets, anticoagulants, antifibrins, and antithrombins include sodium heparin, low molecular weight heparin, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogs, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist, recombinant hirudin, thrombin inhibitor (available from Biogen), and 7E-3B® (an antiplatelet drug from Centocore). Examples of suitable antimitotic agents include methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, adriamycin, and mutamycin. Examples of suitable cytostatic or antiproliferative

agents include angiopeptin (a somatostatin analog from Ibsen), angiotensin converting enzyme inhibitors such as CAPTOPRIL (available from Squibb), CILAZAPRIL (available from Hoffman-LaRoche), or LISINOPRIL (available from Merck); calcium channel blockers (such as Nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), histamine antagonist, LOVASTATIN (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug from Merck), monoclonal antibodies (such as PDGF receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitor (available form Glazo), Seramin (a PDGF antagonist), serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. Other therapeutic substances or agents which may be appropriate include alpha-interferon, genetically engineered epithelial cells, and dexamethasone. Exposure of the composition to the active ingredient is not permitted to adversely alter the active ingredient's composition or characteristic. Accordingly, the particular active ingredient is selected for mutual compatibility with the blended composition.

[0063] The dosage or concentration of the active ingredient required to produce a favorable therapeutic effect should be less than the level at which the active ingredient produces toxic effects and greater than the level at which non-therapeutic results are obtained. The dosage or concentration of the active ingredient required to inhibit the desired cellular activity of the vascular region can depend upon factors such as the particular circumstances of the patient; the nature of the trauma; the nature of the therapy desired; the time over which the ingredient administered resides at the vascular site; and if other bioactive substances are employed, the nature and type of the substance or combination of substances. Therapeutic effective dosages can be determined empirically, for example by infusing vessels from suitable animal model systems and using immunohistochemical, fluorescent or electron microscopy methods to detect the agent and its effects, or by conducting suitable in vitro studies. Standard pharmacological test procedures to determine dosages are understood by one of ordinary skill in the art.

[0064] By way of example, the polymer can comprise from about 0.1% to about 35%, more narrowly from about 2% to about 20% by weight of the total weight of the composition, the solvent can comprise from about 59.9% to about 99.8%, more narrowly from about 79% to about 87% by weight of the total weight of the composition, and the active ingredient can comprise from about 0. 1% to about 40%, more narrowly from about 1% to about 9% by weight of the total weight of the composition. More than 9% by weight of the active ingredient could adversely affect characteristics that are desirable in the polymeric coating, such as adhesion of the coating to the device. With the use of the primer layer, weight ratios of more than 9% for the active ingredient are achievable. Selection of a specific weight ratio of the polymer and solvent is dependent on factors such as, but not limited to, the material from which the device is made, the geometrical structure of the device, and the type and amount of the active ingredient employed. The particular weight percentage of the active ingredient mixed within the composition depends on factors such as duration of the release, cumulative amount of release, and release rate that is desired.

[0065] Optionally, a second fluid or solvent, such as tetrahydrofuran (THF) or dimethylformamide (DMF) can be used to improve the solubility of an active ingredient in the composition and/or to increase the wetting of the composition. Increasing the wetting of the composition has been discovered to lead to the application of a more uniformed coating. The second fluid or solvent can be added to the composition or the active ingredient can be added to the second solvent prior to admixture with the blend.

[0066] In this embodiment with a second fluid, by way of example, the polymer can comprise from about 0.1% to about 35%, more narrowly from about 2% to about 20% by weight of the total weight of the composition, the solvent can comprise from about 19.8% to about 98.8%, more narrowly from about 49% to about 79% by weight of the total weight of the composition, the second solvent can comprise from about 1% to about 80%, more narrowly from about 5% to about 40% by weight of the total weight of the composition, and the active ingredient can comprise from about 0.1% to about 40%, more narrowly from about 1% to about 9% by weight of the total weight of the composition. Selection of a specific weight ratio of the polymer, the solvent, and the second solvent is dependent on factors such as, but not limited to, the material from which the implantable device is made, the geometrical structure of the device, and the type and amount of the active ingredient employed. The particular weight percentage of the active ingredient mixed within the composition depends on factors such as duration of the release, cumulative amount of release, and release rate that is desired.

[0067] Table 2 is an exemplary list of suitable combinations in accordance with various embodiment of the present invention:

TABLE 2

POLYMER	SOLVENT	SECOND SOLVENT	ACTIVE INGREDIENT
EVOH (29 mol % ethylene content e.g., Soarnol ®)	IPA/H_2O (1:1)	—	Actinomycin D
EVOH (44 mol % ethylene content)	DMSO	THF	Actinomycin D
EVOB	DMSO	THF	Actinomycin D
EVOH	DMSO	DMF	Paclitaxel
poly(L-lactic acid)	chloroform	—	dexamethasone
poly(lactic acid-co-glycolic acid)	acetone	—	dexamethasone
Polyether urethane	N-methyl pyrrolidinone	—	tocopherol

Composition for Forming The Rate Reducing Membrane

[0068] The embodiments of the composition for a rate-reducing membrane or diffusion barrier layer are prepared by conventional methods wherein all components are combined. In the embodiment with the use of particles, dispersion techniques should also be employed to circumvent agglomeration or formation of particle flocs.

[0069] More particularly, in accordance with one embodiment, the embodiments for the composition for the reservoir layer can be applied on a selected region of the reservoir layer to form a rate reducing member or a barrier layer. The

barrier layer can reduce the rate of release or delay the time at which the active ingredient is released from the reservoir layer. In one embodiment, for maximum blood compatibility, polyethylene glycol or polyethylene oxide can also be added to the blend. Ethylene vinyl alcohol is functionally a very suitable choice of polymer. The copolymer allows for good control capabilities over the release rate of the active ingredient. As a general rule, an increase in the amount of the ethylene comonomer content decreases the rate that the active ingredient is released from the copolymer matrix. The release rate of the active ingredient decreases as the hydrophilicity of the polymer decreases. An increase in the amount of the ethylene comonomer content increases the overall hydrophobicity of the copolymer, especially as the content of vinyl alcohol is concomitantly reduced.

[0070] Usefully, the choice of polymer for the barrier layer can be the same as the selected polymer for the reservoir. The use of the same polymer, as described for some of the embodiments, significantly reduces or eliminates any interfacial incompatibilities, such as lack of adhesion, which may exist in the employment of two different polymeric layers. In effect, it can be said that the use, if desired, of the same polymeric material for the barrier layer and the reservoir layer results in the formation of a single-layered coating. In other words, the use of the same polymeric material results in a seamless multi-layered coating in which the layers vary in terms of their content. Defined interfacial boundaries are, accordingly, significantly reduced or eliminated.

[0071] In accordance with another embodiment, particles of inorganic or organic type are added to the blend. The particles should be dispersed in the blend. Dispersed is defined as the particles being present as individual particles, not agglomerates or flocs. In certain polymer-solvent blends, certain particles will disperse with ordinary mixing. Otherwise the particles can be dispersed in the composition by high shear processes such as ball mill, disc mill, sand mill, attritor, rotor stator mixer, ultrasonication—all such high shear dispersion techniques being well known to one of ordinary skill in the art. Optionally, one of the aforementioned wetting fluids can also be added to the blend. The wetting fluid can be added prior to, contemporaneously with, or subsequent to the agitation. Biocompatible dispersing agents in the form of surfactants, emulsifiers, or stablilizers may also be added to the blend to assist in particle dispersion.

[0072] The particles can be made from any suitable material having barrier-type properties, such as, but not limited to tortuousity, excluded volume, and adsorptivity. Tortuosity refers to the exclusion of space in the polymer matrix for the creation of a defined space or a tortuous path through and about which the active ingredient must travel to be expelled from the layer. Excluded volume refers to the volume displaced by the particles that would otherwise be available for the diffusion of the active ingredient. Adsorptivity refers to the chromatographic effect which is dependent upon the interaction between the active ingredient used in combination with the particle. The active ingredient may be partially adsorbed and released by the surface of the particles, such as silica or fumed carbon particles.

[0073] In one embodiment, the particles can be made from a metal oxide, such as rutile titanium oxide, anatase titanium dioxide, niobium oxide, tantalum oxide, zirconium oxide, iridium oxide, or tungsten oxide. In another embodiment, the particles can be made from a main group oxide such as silica (silicon oxide) or alumina (aluminum oxide). Metallic particles such as gold, hafnium, platinum, iridium, palladium, tungsten, tantalum, niobium, zirconium, titanium, aluminum, or chromium can also be employed. In another embodiment, carbonaceous particles made from, for example, lamp black, furnace black, carbon black, famed carbon black, gas black, channel black, activated charcoal, diamond, diamond like carbon, or CVD diamond can be employed. In yet another embodiment, the particles can be made from nitrides such as titanium nitride, chromium nitride, and zirconium nitride. In yet another embodiment, carbides such as tungsten carbide, silicon carbide, or titanium carbide, and calcium salts such as hydroxyapatite, dahlite, brushite, tricalcium phosphate, calcium sulphate, and calcium carbonate can be used. Other inorganic particles can include particles made from silicides, barium titanate, and strontium titanate.

[0074] In yet another embodiment, the particles can be made from a suitable polymer including polymers of polyolefins, polyurethanes, cellulosics (i.e., polymers having mer units derived from cellulose), polyesters, polyamides, poly(hexamethylene isophthalamide/terephthalamide) (commercially available as SELAR PA™), poly(ethylene terephthalate-co-p-oxybenzoate) (PET/PHB, e.g., copolymer having about 60-80 mole percent PHB), poly(hydroxy amide ethers), polyacrylates, polyacrylonitrile, acrylonitrile/styrene copolymer (commercially available as LOPAC), rubber-modified acrylonitrile/acrylate copolymer (commercially available as BAREX), poly(methyl methacrylate), liquid crystal polymers (LCP) (e.g., VECTRA available from Hoescht-Celanese, ZENITE available from DuPont, and XYDAR available from Amoco Performance Chemicals), poly(phenylene sulfide), polystyrenes, polycarbonates, poly(vinyl alcohols), poly(ethylene-vinyl alcohol) (EVOH, e.g., having about 27 to about 47 mole percent of ethylene content), epoxies composed of bisphenol A based diepoxides with amine cure, aliphatic polyketones (e.g., CARILON available from Shell, and KETONEX available from British Petroleum), polysulfones, poly(ester-sulfone), poly(urethane-sulfone), poly(carbonate-sulfone), poly(3-hydroxyoxetane), poly(amino ethers), gelatin, amylose, parylene-C, parylene-D, parylene-N.

[0075] Representatives polyolefins include those based upon alpha-monoolefin monomers having from about 2 to 6 carbon atoms and halogen substituted olefins, i.e., halogenated polyolefins. By way of example, and not limitation, low to high density polyethylenes, essentially unplasticized poly (vinyl chloride), poly (vinylidene chloride), poly (vinyl fluoride), poly (vinylidene fluoride), poly (tetrafluoroethylene) (Teflon), poly (chlorotrifluoroethylene) (KEL-F), and mixtures thereof are suitable. Low to high density polyethylenes are generally understood to have densities of about 0.92 g cm^{-3} to about 0.96 g cm^{-3}, however, no bright line can be drawn for density classifications and the density can vary according to the supplier.

[0076] Representative polyurethanes include polyurethanes having a glass transition temperature above a storage or ambient temperature, for example having a glass transition temperature of at least 40° C. to 60° C., or having a non-polar soft segment which includes a hydrocarbon, silicone, fluorosilicone, or mixtures thereof. For example,

ELAST-EON, manufactured by Elastomedic/CSIRO Molecular Science, is a polyurethane with a non-polar soft segment which is made from 1,4-butanediol, 4,4'-methylenediphenyl diisocyanate, and a soft segment composed of a blend poly(hexamethylene oxide) (PHMO) and bishydroxyethoxypropylpolydimethylsiloxane (PDMS). A useful example has a blend of 20% by weight PHMO and 80% by weight PDMS.

[0077] Representative examples of cellulosics include, but are not limited to, cellulose acetate having a degree of substitution (DS) greater than about 0.8 or less than about 0.6, ethyl cellulose, cellulose nitrate, cellulose acetate butyrate, methyl cellulose, and mixtures thereof.

[0078] Representative polyesters include saturated or unsaturated polyesters such as, but not limitated to, poly (butylene terephthalate), poly(ethylene 2,6-naphthalene dicarboxylate) (PEN), and poly (ethylene terephthalate).

[0079] Representative polyamides include crystalline or amorphous polyamides such as, but not limited to, nylon-6, nylon-6,6, nylon-6,9, nylon-6,10, aromatic nylon MXD6 (manufactured by Mitsubishi Gas Chemical America Inc.), and mixtures thereof.

[0080] Representative polyacrylates include, but are not limited to, poly(methylmethacrylate) and polymethacrylate.

[0081] In one embodiment, the particle can be a mixture of the aforementioned polymers. For example, the polymer can comprise about 70% to about 99% by weight acrylonitrile and about 30% to about 1% by weight styrene. Similarly, copolymers of vinyl chloride and vinylidene chloride with a vinyl chloride content of about 1 to about 30 mole percent and PET/PHB copolymers with a PHB content of about 60 to about 80 mole percent function effectively.

Examples of the Device

[0082] The device or prosthesis used in conjunction with the above-described compositions may be any suitable device used for the release of an active ingredient, examples of which include self-expandable stents, balloon-expandable stents, and stent-grafts, and grafts. The underlying structure of the device can be virtually any design. The device can be made of a metallic material or an alloy such as, but not limited to, cobalt chromium alloy (ELGILOY), stainless steel (316L), "MP35N,""MP20N," ELASTINITE (Nitinol), tantalum, nickel-titanium alloy, platinum-iridium alloy, gold, magnesium, or combinations thereof. "MP35N" and "MP20N" are trade names for alloys of cobalt, nickel, chromium and molybdenum available from standard Press Steel Co., Jenkintown, Pa. "MP35N" consists of 35% cobalt, 35% nickel, 20% chromium, and 10% molybdenum. "MP20N" consists of 50% cobalt, 20% nickel, 20% chromium, and 10% molybdenum. Devices made from bioabsorbable or biostable polymers could also be used with the embodiments of the present invention. A polymeric device should be compatible with the selected compositions. The ethylene vinyl alcohol copolymer, however, adheres very well to metallic materials, more specifically to stainless steel.

Methods For Applying the Compositions to the Device

[0083] To form the primer layer, the surface of the device or prosthesis should be clean and free from contaminants that may be introduced during manufacturing. However, the surface of the prosthesis requires no particular surface treatment to retain the applied coating. Metallic surfaces of stents can be, for example, cleaned by argon plasma process as is well known to one of ordinary skill in the art. Application of the composition can be by any conventional method, such as by spraying the composition onto the prosthesis or immersing the prosthesis in the composition. Operations such as wiping, centrifugation, blowing, or other web clearing acts can also be performed to achieve a more uniform coating. Briefly, wiping refers to physical removal of excess coating from the surface of the stent; centrifugation refers to rapid rotation of the stent about an axis of rotation; and blowing refers to application of air at a selected pressure to the deposited coating. The excess coating can also be vacuumed off the surface of the device. The addition of a wetting fluid leads to a consistent application of the composition, which also causes the coating to be uniformly deposited on the surface of the prosthesis.

[0084] With the use of the thermoplastic polymers, such as ethylene vinyl alcohol copolymer, polycaprolactone, poly-(lactide-co-glycolide), poly(hydroxybutyrate), etc., the deposited primer composition should be exposed to a heat treatment at temperature range greater than about the glass transition temperature (T_g) and less than about the melting temperature (T_m) of the selected polymer. Unexpected results have been discovered with treatment of the composition under this temperature range, specifically strong adhesion or bonding of the coating to the metallic surface of a stent. The device should be exposed to the heat treatment for any suitable duration of time, which would allow for the formation of the primer coating on the surface of the device and allows for the evaporation of the solvent or combination of solvent and wetting fluid. It is understood that essentially all of the solvent and the wetting fluid will be removed from the composition but traces or residues can remain blended with the polymer.

[0085] Table 3 lists the T_g and T_m for some of the polymers used in the embodiments of the present invention. T_g and T_m of polymers are attainable by one or ordinary skill in the art. The cited exemplary temperature and time for exposure is provided by way of illustration and it is not meant to be limiting.

TABLE 3

Polymer	T_g (° C.)	T_m (° C.)	Exemplary Temperature (° C.)	Exemplary Duration of Time For Heating
EVOH	55	165	140	4 hours
polycaprolactone	−60	60	50	2 hours
ethylene vinyl acetate (e.g., 33% vinylacetate content)	36	63	45	2 hours
Polyvinyl alcohol	75–85*	200–220*	165	2 hours

*Exact temperature depends on the degree of hydrolysis which is also known as the amount of residual aceatate.

[0086] With the use of one of the aforementioned thermoset polymers, the use of initiators may be required. By way of example, epoxy systems consisting of diglycidyl ether of

bisphenol A resins can be cured with amine curatives, thermoset polyurethane prepolymers can cured with polyols, polyamines, or water (moisture), and acrylated urethane can be cured with UV light. Examples 27 and 28 provide illustrative descriptions. If baked, the temperature can be above the T_g of the selected polymer.

[0087] With the use of the inorganic polymers, such as silanes, titanates, and zirconates the composition containing the prepolymer or precursor is applied and the solvent is allowed to evaporate. Example 29 provides a brief description.

[0088] Subsequent to the formation of the primer layer, the composition containing the active ingredient can be applied to a designated region of the primer coating. Masking techniques can be implemented for applying compositions containing different active ingredients to selected regions of the primer layer. Accordingly, stents having various cocktail formulations or combinations of a variety of active ingredients can be manufactured. The solvent(s) or the combination of the solvent(s) and the wetting fluid is removed from the composition by allowing the solvent(s) or combination of the solvent(s) and the wetting fluid to evaporate. The evaporation can be induced by heating device at a predetermined temperature for a predetermined period of time. For example, the device can be heated at a temperature of about 60° C. for about 12 hours to about 24 hours. The heating can be conducted in an anhydrous atmosphere and at ambient pressure and should not exceed the temperature which would adversely affect the active ingredient. The heating can, alternatively, be conducted under a vacuum condition. It is understood that essentially all of the solvent and the wetting fluid will be removed from the compositision but traces or residues can remain blended with the polymer.

[0089] The diffusion barrier layer can be deposited on a designated region of the active ingredient-containing coating subsequent to the evaporation of the solvent(s) or solvent(s)/wetting fluid and the drying of the polymer for the active ingredient-containing coating. The diffusion barrier layer can also be applied by spraying the composition onto the device or immersing the device in the composition. The above-described processes can be similarly repeated for the formation of the diffusion barrier layer.

Coating

[0090] Some of the various embodiments of the present invention are illustrated by FIGS. 2A-2E, 3A and 3B. The Figures have not been drawn to scale, and the depth and thickness of the various regions and layers have been over or under emphasized for illustrative purposes.

[0091] Referring to **FIG. 2A, a** body of a stent **20** is illustrated having a surface **22**, e.g., metallic surface such as stainless steel. A coating **24** is disposed on surface **22**. Coating **24** includes a first region **26** defining the reservoir portion of coating **24** containing the active ingredient. A second region **28**, free from any active ingredients, defines the primer portion of coating **24**. In accordance with another embodiment, as illustrated in **FIG. 2**B, coating **24** can include a third region **30** defining a barrier portion, free from any particles. Third region **30**, as illustrated in **FIG. 2**C, can also include particles **32**.

[0092] Coating **24** for FIGS. **2A-2**C is made from only one of the aforementioned polymeric materials, e.g., EVOH, and accordingly, the existence of any interfacial boundaries between the fist **26**, second **28**, and third **30** regions is essentially reduced or eliminated. Elimination of interfacial boundaries essentially reduces or eliminates any incompatibilities, such as adhesiveness, that may exist when using layers of different polymeric materials.

[0093] By way of example, and not limitation, reservoir region **26** for coating **24** can have a thickness T_1 of about 0.5 microns to about 10 microns. The particular thickness T_1 is based on the type of procedure for which stent **20** is employed and the amount of the active ingredient that is desired to be delivered. Primer region **28** can have any suitable thickness T_2, examples of which can be in the range of about 0.1 to about 10 microns, more narrowly about 0.1 to about 2 microns. Diffusion barrier region **30** can have any suitable thickness T_3, as the thickness T_3 is dependent on parameters such as, but not limited to, the desired rate or duration of release and the procedure for which stent **20** will be used. Diffusion barrier region **30** can have a thickness T_3 of about 0.1 to about 10 microns, more narrowly from about 0.25 to about 2 microns. If particles **32** are employed, for a smooth outer surface, the size of particles **32** should not be greater than about 10% of thickness T_3 of diffusion barrier region **30**. Additionally, the particle volume fraction X_p should not exceed about 0.74. Packing density or particle volume fraction X_p can be defined by the following equation:

$$X_p = V_{particles}/(V_{particles}+V_{polymer})$$

[0094] wherein V is volume.

[0095] In yet another embodiment, as illustrated in **FIG. 2**D, reservoir region **26** can include a first and second reservoir sections **26**A and **26**B, each containing a different active ingredient, e.g., actinomycin D and taxol, respectively. Accordingly, coating **24** can carry a combination of at least two different active ingredients for sustained delivery. First and second sections **26**A and **26**B can be deposited by, for example, masking the area of primer region **28** over second section **26**B and applying a first composition containing a first active ingredient to form first section **26**A. First section **26**A can them be masked and a second composition containing a second active ingredient can be applied to form second section **26**B. This procedure can be followed to from any suitable number of regions containing a different active ingredient.

[0096] In accordance with yet another embodiment, barrier region **30** can be formed on reservoir sections **26**A and **26**B, as illustrated in **FIG. 2D**. Referring to **FIG. 2**E, barrier region **30** can include a first barrier section **30**A disposed over first reservoir section **26**A containing a first active ingredient, e.g., actinomycin D. A second barrier section **30**B is formed over second reservoir section **26**B containing a second active ingredient, e.g., taxol. First barrier section **30**A is particle free and second barrier section **30**B contains particles **32**. As a result, coating **24** harbors two different release parameters for each of the active ingredients contained in reservoir sections **26**A and **26**B.

[0097] In accordance with yet another embodiment, different polymeric materials having interfacial compatibilities can be used to form individual, distinct layers for the primer,

reservoir, and diffusion barrier components of the coating. Referring to **FIG. 3A, a** coating **34** is provided having a primer layer **36**, made from a first polymeric material, formed on surface **22** of stent **20**. A reservoir layer **38** made from a second polymeric material is deposited on a selected area of primer layer **36**. A barrier layer **40**, made from a third polymeric material can be deposited on reservoir layer **38**.

[0098] One of ordinary skill in the art can appreciate that a variety of coating combinations can be provided with the practice of the present invention. For example, as illustrated in **FIG. 3**B, coating **34** contains primer layer **36** made from a first polymeric material. Reservoir layer **38**, made from a second polymeric material, is formed on primer layer **36**. Reservoir layer **38** contains first and second regions, illustrated as **38**A and **38**B. First and second regions **38**A and **38**B each contain a different active ingredient. Barrier layer **40**, made from a third polymeric material, can be deposited on reservoir layer **38**. Barrier layer **40** includes a first region **40**A deposited over first region **38**A of reservoir layer **38**. Barrier layer **40** additionally includes a second region **40**B deposited over second region **38**B of reservoir layer **38**. Second region **40**B can include particles **32** and/or be made out of a fourth polymeric material to create a variety of different release parameters.

[0099] Examples of different polymeric materials having interfacial compatibilities include, for example, an EVOH primer with a reservoir layer of ethylene vinylacetate; a poly(n-butyl methacrylate) primer with an EVOH reservoir layer; an EVOH primer and a reservoir layer of polycaprolactone; and an epoxy primer consisting of the diglycidylether of bisphenol A cured with polyamine curatives with an EVOH reservoir layers. Other combinations can be derived by one of ordinary skill in the art.

Method of Use

[0100] In accordance with the above-described method, the active ingredient can be applied to a medical device, e.g., a stent, retained on the stent during delivery and expansion of the stent, and released at a desired control rate and for a predetermined duration of time at the site of implantation. A stent having the above-described coating layers is useful for a variety of medical procedures, including, by way of example, treatment of obstructions caused by tumors in bile ducts, esophagus, trachea/bronchi and other biological passageways. A stent having the above-described coating layers is particularly useful for treating occluded regions of blood vessels caused abnormal or inappropriate migration and proliferation of smooth muscle cells, thrombosis, and restenosis. Stents may be placed in a wide array of blood vessels, both arteries and veins. Representative examples of sites include the iliac, renal, and coronary arteries. The application of the present invention should not, however, be limited to stents such that the embodiments of the coating can be used with a variety of medical substrates.

[0101] Briefly, an angiogram is first performed to determine the appropriate positioning for stent therapy. Angiography is typically accomplished by injecting a radiopaque contrast agent through a catheter inserted into an artery or vein as an x-ray is taken. A guidewire is then advanced through the lesion or proposed site of treatment. Over the guidewire is passed a delivery catheter which allows a stent in its collapsed configuration to be inserted into the passageway. The delivery catheter is inserted either percutaneously or by surgery into the femoral artery, brachial artery, femoral vein, or brachial vein, and advanced into the appropriate blood vessel by steering the catheter through the vascular system under fluoroscopic guidance. A stent having the above described coating layers may then be expanded at the desired area of treatment. A post insertion angiogram may also be utilized to confirm appropriate positioning.

EXAMPLES

[0102] The embodiments of the invention will be illustrated by the following set forth examples which are being given by way of illustration only and not by way of limitation. All parameters and data are not be construed to unduly limit the scope of the embodiments of the invention.

Example 1

[0103] Multi-Link™ stents (available from Guidant Corporation) were cleaned by placement in an ultrasonic bath of isopropyl alcohol solution for 10 minutes. The stents were dried and plasma cleaned in a plasma chamber. An EVOH solution was made with 1 gram of EVOH and 7 grams of DMSO, making an EVOH: DMSO ratio of 1:7. The mixture was placed in a warm water shaker bath at 60° C. for 24 hours. The solution was cooled and vortexed. The cleaned Multi-Link™ stents were dipped in the EVOH solution and then passed over a hot plate, for about 3-5 seconds, with a temperature setting of about 60° C. The coated stents were heated for 6 hours in an air box and then placed in an oven at 60° C., under vacuum condition, and for 24 hours. The coated stents were expanded on a 4.0 mm angioplasty balloon. The coatings remained intact on the stents. The coatings were transparent giving the Multi-Link™ stents a glossy-like shine.

Example 2

[0104] Multi-Link™ stents were cleaned by placement in an ultrasonic bath of isopropyl alcohol solution for 10 minutes. The stents were dried and plasma cleaned in a plasma chamber. An EVOH solution was made with 1 gram of EVOH and 4 grams of DMSO, making an EVOH:DMSO ratio of 1:4. Dexamethasone was added to the 1:4 EVOH:DMSO solution. Dexamethasone constituted 9% by weight of the total weight of the solution. The solution was vortexed and placed in a tube. The cleaned Multi-Link™ stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3-5 seconds, with a temperature setting of about 60° C. The coated stents were cured for 6 hours in an air box and then placed in a vacuum oven at 60° C. for 24 hours. The above-recited step was repeated twice. The average weight of the coating was 0.0003 gram, having an estimated dexamethasone content of 75 ug per stent. The coated stents were expanded on a 4.0 mm angioplasty balloon. The coatings remained intact on the stents. Verification of coverage and physical properties of the coatings were visualized using a scanning electron microscope. The coatings were transparent, giving the Multi-Link™ stents a glossy-like shine.

Example 3

[0105] Multi-Link Duet™ stents are cleaned by placement in an ultrasonic bath of isopropyl alcohol solution for 10

minutes. The stents are dried and plasma cleaned in a plasma chamber. The EVOH solution is made with 1 gram of EVOH and 4 grams of DMSO, making an EVOH:DMSO ratio of 1:4. Dexamethasone is added to the 1:4 EVOH:DMSO solution. Dexamethasone constitutes 9% by weight of the total weight of the solution. The solution is vortexed and placed in a tube. The cleaned Multi-Link™ stents are attached to mandrel wires and dipped into the solution. The coated stents are passed over a hot plate, for about 3-5 seconds, with a temperature setting of about 60° C. The coated stents are cured for 6 hours in an air box then placed in a vacuum oven at 60° C. for 24 hours. The single layered dexamethasone/EVOH coated stents are dipped into the 1:4 ratio EVOH:DMSO solution, free from dexamethasone. The stents are passed over the hot plate, cured, and placed in the oven as previously described. The top coating will provide a barrier layer for controlling the release of dexamethasone from the drug coated layer. The coated stents can be expanded on a 4.0 mm angioplasty balloon. It is predicted that the coatings will remain intact on the stents. The coatings will be transparent, giving the Multi-Link™ stents a glossy-like shine.

Example 4

[0106] Multi-Link™ stents were cleaned by placement in an ultrasonic bath of isopropyl alcohol solution for 10 minutes. The stents were dried and plasma cleaned in a plasma chamber. An EVOH solution was made with 1 gram of EVOH and 7 grams of DMSO, making an EVOH:DMSO ratio of 1:7. Vinblastine was added to the 1:7 EVOH:DMSO solution. Vinblastine constituted 2.5% by weight of the total weight of the solution. The solution was vortexed and placed in a tube. The cleaned Multi-Link™ stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3-5 seconds, with a temperature setting of about 60° C. The coated stents were cured for 6 hours in an air box then placed in a vacuum oven at 60° C. for 24 hours. The above process was repeated twice, having a total of three layers. The average weight of the coating was 0.00005 gram, with an estimated vinblastine concentration of 12 microgram per stent. Some of the stents were sterilized by electron beam radiation. The sterilized and unsterilized vinblastine coated stents were tested for a 24 hour elution period by placing one sterilized and one unsterilized stent in 5 ml of phosphated saline solution (pH 7.4) at room temperature with rotational motion. The amount of vinblastine eluted was evaluated by High Performance Liquid Chromatography (HPLC) analysis. The results of this test are given below and plotted in **FIG. 4**. The data indicates that electron beam radiation procedure does not interfere in the release of vinblastine from EVOH.

Release Profile For Vinblastine -- Unsterilized

Time (Hours)	microgram Released	Total microgram Released	microgram Release per Hour
0	0	0	0
0.5	2.12	2.12	4.24
3	1.91	4.03	0.76
4	0.27	4.30	0.27

-continued

Release Profile For Vinblastine -- Unsterilized

Time (Hours)	microgram Released	Total microgram Released	microgram Release per Hour
6	0.38	4.68	0.19
24	1.7	6.38	0.09

[0107]

Release Profile For Vinblastine -- Sterilized

Time (Hours)	ug Release	Total uG Released	uG Release per Hour
0	0	0	0
0.5	2.14	2.14	4.28
3	1.7	3.84	0.68
4	0.28	4.12	0.28
6	0.26	4.38	0.13
24	2.05	6.43	0.11

Example 5

[0108] Multi-Link™ stents were cleaned by placement in an ultrasonic bath of isopropyl alcohol solution for 10 minutes. The stents were dried and plasma cleaned in a plasma chamber. An EVOH solution was made with 1 gram of EVOH and 7 grams of DMSO, making an EVOH:DMSO ratio of 1:7. Cephalotaxin was added to the 1:7 EVOH:DMSO solution. Cephalotaxin constituted 5% by weight of the total weight of the solution. The solution was vortexed and placed in a tube. The cleaned Multi-Link™ stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3-5 seconds, with a temperature setting of about 60° C. The coated stents were cured for 6 hours in an air box then placed in a vacuum oven at 60° C. for 24 hours. The above process was repeated twice, having a total of three layers. The average weight of the coating was 0.00013 gram, with an estimated cephalotaxin concentration of 33 ug. The stents were sterilized by electron beam radiation. Cephalotaxin/EVOH coated stents and EVOH-coated control stents were implanted in the coronary arteries of 4 pigs, generally in accordance to the procedure set forth in "Restenosis After Balloon Angioplasty—A Practical Proliferative Model in Porcine Coronary Arteries" by Robert S. Schwartz, et al., Circulation 82(6):2190-2200, December 1990, and "Restenosis and the Proportional Neointimal Response to Coronary Artery Injury: Results in a Porcine Model" by Robert S. Schwartz et al, J Am Coll Cardiol; 19:267-74 February 1992. Results of the porcine artery study indicated that there was no significant difference between the uncoated, EVOH coated and cephalotaxin coated stents in the amount of neointimal proliferation resulting from arterial injury.

Example 6

[0109] Multi-Link Duet™ stents (available from Guidant Corporation) were cleaned by placement in an ultrasonic bath of isopropryl alcohol solution for 20 minutes, then air dried. An EVOH stock solution was made with 1 gram of EVOH and 7 grams of DMSO, making an EVOH:DMSO

ratio of 1:7. The mixture was placed in a warm water shaker bath at 60° C. for 12 hours. The solution was mixed, then cooled to room temperature. A co-solvent was added to the EVOH solution to promote wetting of the struts of the Multi-Link Duet™ stents. One gram of tetrahydrofuran (THF) was mixed with 1.2 grams of the EVOH:DMSO solution. The cleaned Multi-Link Duet™ stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3 to 5 seconds, with a temperature setting of about 60° C. The coated stents were then heated in a laboratory oven at 90° C. for 4 hours. The thin EVOH coating adhered to stainless steel without peeling or cracking. EVOH forms a superior primer base coat for other polymers that do not adhere well to stainless steel.

Example 7

[0110] Multi-Link Duet™ stents were cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVOH solution was made with 1 gram of EVOH and 5 grams of DMSO, making an EVOH:DMSO ratio of 1:5. The mixture was placed in a warm water shaker bath at 60° C. for 12 hours. The solution was mixed, then cooled to room temperature. The dissolved EVOH:DMSO solution was mixed with 24.6 grams of THF and 19.56 grams of DMSO. The solution was mixed then placed in the reservoir of an air pressured atomizing sprayer. Multi-Link Duet™ stents were sprayed while the stents rotated between 30 to 120 rpm. The spray time was dependent upon the flow rate of the sprayer. A flow rate between 1 to 20 mg/second required a stent to be sprayed between 1 to 30 seconds. The polymer coated Multi-Link Duet™ stents were heated in a forced air convection oven for 12 hours. The coatings were transparent, giving the Multi-Link Duet™ stents a glossy-like shine.

Example 8

[0111] Multi-Link Duet™ stents were cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVOH stock solution was made having an EVOH:DMSO ratio of 1:4. The mixture was placed in a warm water shaker bath at 60° C. for 12 hours. The solution was mixed, then cooled to room temperature. Various co-solvents were examined to determine which co-solvent would promote a thicker coating. These co-solvents were THF, DMF, 1-butanol, and n-butyl acetate. The formulation for the co-solvents was as follows. Three grams of dissolved EVOH:DMSO solution was mixed with 0.9 gram of THF; three grams of dissolved EVOH:DMSO solution was mixed with 0.39 gram of DMF; three grams of dissolved EVOH:DMSO solution was mixed with 0.5 gram of 1-butanol; and three grams of dissolved EVOH:DMSO solution was mixed with 0.68 gram of n-butyl acetate. The cleaned Multi-Link Duet™ stents, attached to mandrel wires, were dipped into the solutions. The coated stents were passed over a hot plate, for about 3 to 5 seconds, with a temperature setting of about 60° C. The coated stents were heated in a forced air convection oven for 24 hours. A second layer of coating was applied to coated Multi-Link Duet™ stents and the stents were heated in the same manner as above. No difference was seen between the stents coated with the various co-solvents (e.g., greater weight of coating or physical appearance). All coated stents were transparent, giving the Multi-Link Duet™ stents a glossy-like shine. No webbing or bridging of the coating was seen between the struts of the coated Multi-Link Duet™ stents. The weight of the coatings was between 0.2 to 0.27 mg/stent.

Example 9

[0112] Multi-Link Duet™ stents are cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVOH stock solution is made having an EVOH:DMSO ratio of 1:4. The mixture is placed in a warm water shaker bath at 60° C. for 12 hours. The solution is mixed, then cooled to room temperature. A 9% by weight Dexamethasone solution is formulated as follows: 2.96 grams of the EVOH:DMSO solution is mixed with 0.29 gram of Dexamethasone, then 0.9 gram of THF is added. The cleaned Multi-Link Duet™ stents are attached to mandrel wires and dipped into the solution. The coated stents are passed over a hot plate, for about 3 to 5 seconds, with a temperature setting of about 60° C. The coated stents are cured in a forced air convection oven for 2 hours. A second layer of coating is applied and cured in the above manner. It is predicted that the coatings will be transparent, giving the Multi-Link Duet™ stents a glossy-like shine.

Example 10

[0113] Multi-Link Duet™ stents are cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVOH stock solution is made having an EVOH:DMSO ratio of 1:4. The mixture is placed in a warm water shaker bath at 60° C. for 12 hours. The solution is mixed, then cooled to room temperature. A 9% by weight Dexamethasone solution is formulated as follows: 2.96 grams of the EVOH:DMSO solution is mixed with 0.29 gram of Dexamethasone, then 0.9 gram of THF is added. The cleaned Multi-Link Duet™ stents are attached to mandrel wires and dipped into the solution. The coated stents are passed over a hot plate, for about 3 to 5 seconds, with a temperature setting of about 60° C. The coated stents are cured in a forced air convection oven for 2 hours. A second layer of coating is applied and cured in the above manner. It is predicted that the coatings will be transparent, giving the Multi-Link Duet™ stents a glossy-like shine.

Example 11

[0114] Multi-Link Duet™ stents were cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVOH stock solution was made having an EVOH:DMSO ratio of 1:4. The mixture was placed in a warm water shaker bath at 60° C. for 12 hours. The solution was mixed, then cooled to room temperature. A 4.75% by weight actinomycin D solution was formulated as follows: 600 milligrams of the EVOH:DMSO solution was mixed with 40 milligrams of actinomycin D, then 200 milligrams of THF was added. The cleaned Multi-Link Duet™ stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3 to 5 seconds, with a temperature setting of about 60° C. The coated stents were cured in a forced air convection oven for 2 hours. A second layer of coating was applied and cured in the above manner.

Example 12

[0115] Multi-Link Duet™ stents were cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air

dried. An EVOH stock solution was made having an EVOH:DMSO ratio of 1:4. The mixture was placed in a warm water shaker bath at 60° C. for 12 hours. The solution was mixed, then cooled to room temperature. A 3.60% by weight actinomycin D solution was formulated as follows: 600 milligrams of the EVOH:DMSO solution was mixed with 40 milligrams of actinomycin D, then 480 milligrams of DMF was added. The cleaned Multi-Link Duet™ stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3 to 5 seconds, with a temperature setting of about 60° C. The coated stents were cured in a forced air convection oven for 2 hours. A second layer of coating was applied and cured in the above manner.

Example 13

[0116] Multi-Link Duet™ stents were cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVOH stock solution was made having an EVOH:DMSO ratio of 1:4. The mixture was placed in a warm water shaker bath at 60° C. for 12 hours. The solution was mixed, then cooled to room temperature. A 6.45% by weight actinomycin D solution was formulated as follows: 680 milligrams of the EVOH:DMSO solution was mixed with 80 milligrams of actinomycin D, then 480 milligrams of DMF was added. The cleaned Multi-Link Duet™ stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3 to 5 seconds, with a temperature setting of about 60° C. The coated stents were cured in a forced air convection oven for 2 hours. A second layer of coating was applied and cured in the above manner.

Example 14

[0117] Multi-Link Duet™ stents are cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVOH stock solution is made having an EVOH:DMSO ratio of 1:40. The mixture is placed in a warm water shaker bath at 60° C. for 12 hours. The solution is mixed, then cooled to room temperature. A 0.60% by weight actinomycin D solution can be formulated as follows: 4920 milligrams of the EVOH:DMSO solution is mixed with 40 milligrams of Actinomycin D, then 2000 milligrams of THF is added. The cleaned Multi-Link Duet™ stents can be sprayed upon by the above formulation. The coated stents are cured in a forced air convection oven for 2 hours. A second layer of coating is applied and cured in the above manner.

Example 15

Inhibition of SMC proliferation with Actinomycin D

[0118] Medial smooth muscle cells (SMC) were isolated from rat aorta and cultured according to explant methods known to one of ordinary skill in the art. Cells were harvested via trypsinization and subcultivated. Cells were identified as vascular SMC through their characteristic hill-and-valley growth pattern as well as indirect immunofluorescence with monoclonal anti SMC α-actin. Studies were performed with cells at passage **3-4**. SMC monlayers were established on 24 well culture dishes, scrape wounded and treated with actinomycin D, mytomycin and docetaxel. The cells were exposed to the drug solution of different concentrations for 2 hours and then washed with buffered saline solution. The proliferation of the cells was quantified by standard technique of thymidine incorporation. The results from the study are tabulated in **FIG. 5**.

[0119] The IC_{50} (concentration at which 50% of the cells stop proliferating) of actimomycin D was $10^{-}9M$ as compared to $5\times10^{-}5M$ for mitomycin and $10^{-}6M$ for docetaxel. Actinomycin D was the most potent agent to prevent SMC proliferation as compared to other pharmaceutical agents.

Example 16

Reduction in Restenosis in the Porcine Coronary Artery Model

[0120] Porcine coronary models were used to assess the degree of the inhibition of neointimal formation in the coronary arteries of a porcine stent injury model by Actinomycin D, delivered with a microporous balloon catheter (1×10^{6} pores/mm^2 with sizes ranging from 0.2-0.8 micron).

[0121] The preclinical animal testing was performed in accordance with the NIH Guide for Care and Use of Laboratory Animals. Domestic swine were utilized to evaluate effect of the drug on the inhibition of the neointimal formation. Each testing procedure, excluding the angiographic analysis at the follow-up endpoints, was conducted using sterile techniques. During the study procedure, the activated clotting time (ACT) was monitored regularly to ensure appropriate anticoagulation. Base line blood samples were collected for each animal before initiation of the procedure. Quantitative coronary angiographic analysis (QCA) and intravascular ultrasound (IVUS) analysis was used for vessel size assessment.

[0122] The vessels at the sites of the delivery were denuded by inflation of the PTCA balloons to 1:1 balloon to artery ratio and moving the balloons back and forth 5 times. The drug was delivered to the denuded sites at 3.5 atm (3.61 Kg/sq cm) for 2 minutes using the microporous balloon catheters before stent deployment. The average volume of delivery was about 3.3±1.2 ml. Following drug delivery, stents were deployed at the delivery site such that final stent to artery ratio was 1.1:1.

[0123] QCA and IVUS analyses were used for stent deployment guidance. Pre-stenting IVUS measurements of the lumen size at the targeted vessel sites were performed for determination of the balloon (size) inflation pressure. Quantitative analysis of the stented coronary arteries to compare pre-stenting, post-stenting, follow-up minimal luminal diameters, stent recoil, and balloon/stent to artery ratio were performed. Following stent implantation and final angiogram, all devices were withdrawn and the wounds closed; the animals were allowed to recover from anesthesia as managed by the attending veterinarian or animal care professionals at the research center.

[0124] Upon return to the research laboratory at the 28-day endpoint, angiographic assessments were performed. Coronary artery blood flow was assessed and the stented vessels were evaluated to determine minimal lumen diameter. The animals were euthanized following this procedure at the endpoint. Following euthanasia, the hearts were pressure perfusion fixed with formalin and prepared for

histological analysis, encompassing light microscopy, and morphometry. Morphometric analysis of the stented arteries included assessment of the position of the stent struts and determination of vessel/lumen areas, percent (%) stenosis, injury scores, intimal and medial areas and intima/media ratios. Percent stenosis is quantitated by the following equation:

100 (IEL area−lumen area)/EEL area

[0125] where IEL is the internal elastic lamia.

[0126] The control group of animals received delivery of water instead of the drug. The test group of animals received actinomycin D in two different concentration of 10^{-5}M and 10^{-4}M. The results of the study are tabulated in Table 4. The percent stenosis in the treated groups (32.3±11.7) was significantly decreased as compared to the control groups (48.8±9.8). **FIGS. 6A and 6B** illustrate sample pictures of the histology slides of the coronary vessels from the control and the Dose 1 group, respectively.

TABLE 4

	CONTROL	DOSE 1	DOSE 2	t test (significant if p < 0.05)	
	0M	1E-05M	1E-04M	p~	p*
	(n = 9)	(n = 10)	(n = 7)		
ANGIOGRAPHIC DATA (QCA)					
Percent Diameter Stenosis	48.8 +/- 9.8	36.8 +/- 9.7	32.3 +/- 11.7	0.02	0.01
	(n = 27)	(n = 30)	(n = 21)		
HISTOMORPHOMETRIC DATA					
Percent Stenosis (IEL area-lumen area)/IEL area	63.4 +/- 12.7	51.8 +/- 13.8	54.1 +/- 11.7	0.002	0.01
Residual Lumen (Lumen area)/IEL area	0.36 +/- 0.16	0.49 +/- 0.14	0.46 +/- 0.08	0.002	0.01

~comparison between control and Dose 1
*comparison between control and Dose 2

[0127] The results of the in vitro and in vivo standard test procedures demonstrate that actinomycin D is useful for the treatment of hyper-proliferative vascular disease. Specifically, actinomycin D is useful for the inhibition of smooth muscle cell hyperplasia, restenosis and vascular occlusion in a mammal, particularly occlusions following a mechanically mediated vascular trauma or injury.

Example 17

[0128] Multi-Link Duet™ stents (13 mm in length) were cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVOH stock solution was made having an EVOH:DMSO ratio of 1:4. The mixture was placed in a warm water shaker bath at 60° C. for 12 hours. The solution was mixed, then cooled to room temperature. A 5.06% by weight actinomycin D solution was formulated as follows: 40 milligrams of actinomycin D was dissolved in 150 milligrams of THF, then 600 milligrams of the EVOH:DMSO was added. The cleaned Multi-Link Duet™ stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3 to 5 seconds, with a temperature setting of about 60° C. The coated stents were cured in a forced air convection oven at 60° C. for 1 hour. A second layer of coating was applied in the above manner and cured in a forced air convection oven at 60° C. for 4 hours. An average coating weight of about 260 micrograms and an average actinomycin D loading of about 64 micrograms was achieved.

Example 18

[0129] Multi-Link Duet™ stents (13 mm in length) were cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVOH stock solution was made having an EVOH:DMSO ratio of 1:4. The mixture was placed in a warm water shaker bath at 60° C. for 12 hours. The solution was mixed, then cooled to room temperature. A 3.75% by weight actinomycin D solution was formulated as follows: 60 milligrams of actinomycin D was dissolved in 310 milligrams of DMF, then 1.22 grams of EVOH:DMSO solution was added. The cleaned Multi-Link Duet™ stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3 to 5 seconds, with a temperature setting of about 60° C. The coated stents were cured in a forced air convection oven at 60° C. for 1 hour. A second layer of coating was applied in the above manner and cured in a forced air convection oven at 60° C. for 4 hours. An average coating weight of about 270 micrograms with an average actinomycin D content of about 51 micrograms was achieved.

Example 19

[0130] Multi-Link Duet™ stents were cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVOH stock solution was made having an EVOH:DMSO ratio of 1:4. The mixture was placed in a warm water shaker bath at 60° C. for 12 hours. The solution was mixed, then cooled to room temperature. A 6.1% by weight actinomycin D solution was formulated as follows: 100 milligrams of actinomycin D was dissolved in 310 milligrams of DMF, then 1.22 grams of EVOH:DMSO was added. The cleaned Multi-Link Duet™ stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3 to 5 seconds, with a temperature setting of about 60° C. The coated stents were cured in a forced air convection oven at 60° C. for 1

hour. A second layer of coating was applied in the above manner and cured in a forced air convection oven at 60° C. for 4 hours. An average coating weight of about 250 micrograms and an average actinomycin D loading of about 75 micrograms was achieved.

Example 20

[0131] Multi-Link Duet™ stents are cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVOH stock solution is made having an EVOH:DMSO ratio of 1:40. The mixture is placed in a warm water shaker bath at 60° C. for 12 hours. The solution is mixed, then cooled to room temperature. A 0.60% by weight actinomycin D solution can be formulated as follows: 4920 milligrams of the EVOH:DMSO solution is mixed with 40 milligrams of Actinomycin D, then 2000 milligrams of THF is added. The cleaned Multi-Link Duet™ stents can be sprayed upon by the above formulation. The coated stents are cured in a forced air convection oven 60° C. for 15 minutes. Additional layers of the coating are applied and cured in the above manner. The final curing step for the coated stents is conducted for about 4 hours.

Example 21

[0132] A stainless steel stent can be spray coated with a formulation of EVOH and a drug, as previously described in any of the above examples. A diffusion barrier composition can be formulated with 2 grams of EVOH blended with 20 grams of dimethylsulfoxide. 2.2 grams of fumed silica can be added and dispersed with a high shear process. With constant agitation, 50 grams of tetrahydrofuran and 30 grams of dimethylformamide are admixed with the blend. The stent, having the EVOH coating, can be immersed in the diffusion barrier composition to form a layer.

Example 22

[0133] A stainless steel stent can be spray coated with a formulation of EVOH and a drug, as previously described in any of the above examples. A diffusion barrier formulation can be made by dissolving 8 grams of EVOH into 32 grams of dimethylsulfoxide. To this is added 14 grams of rutile titanium dioxide and 7 grams more of dimethylsulfoxide. The particles can be dispersed using a ball mill. The final solution is diluted with 39 grams of tetrahydrofuran, added slowly with constant agitation. It is predicted that the diffusion barrier will reduce the rate at which the drug is released from the stent.

Example 23

[0134] A stainless steel stent can be coated with a formulation of EVOH and a drug, as previously described in any of the above examples. A diffusion barrier formulation can be made by dissolving 8 grams of EVOH in 32 grams of dimethylsulfoxide. 10.5 grams of solution precipitated hydroxyapatite can be added to the blend. The particles can be dispersed using a rotor stator mixer. With constant agitation, 30 grams of tetrahydrofuran can be added. The stent can be coated by immersion followed by centrifugation.

Examples 24

[0135] A stent can be coated with a formulation of EVOH and a drug, as previously described in any of the above examples. 8 grams of EVOH can be added 50 grams of dimethylsulfoxide and the polymer can be dissolved by agitation and heat. Four grams of lamp black can be added and dispersed in a ball mill. 60 grams of dimethyl sulfoxide and 110 grams of tetrahydrofuran are slowly added while stirring. The stent can be spray coated.

Example 25

[0136] A stent can be coated with a formulation of EVOH and a drug, as previously described in any of the above examples. Colloidal gold can be prepared by reduction of tetrachloroauric acid with sodium citrate in aqueous solution. The solution can be exchanged by rinsing with tetrahydrofuran. Eight grams of EVOH can be dissolved in 32 grams of dimethylsulfoxide. To this is added a solution of 77 grams of colloidal gold in 32 grams of tetrahydrofuran. The stent can be coated by a dip coating process.

Example 26

[0137] In vivo data is provided illustrated positive remodeling caused by the application of actinomycin D. Stents coated with EVOH impregnated with actinomycin D and a control group of stents coated with EVOH free from actinomycin D were implanted in porcine coronary arteries. The animals were sacrificed at the end of 28 days. The EEL area of the actinomycin D-loaded vessels was statistically significantly greater than the EEL area of the control vessels. The index of remodeling was 1.076 (8.54/7.94).

Condition	Mean Area	Std Dev
IEL		
Drug coated (Act-D in EVOH)	7.47	0.89
Control (EVOH)	6.6	0.61
p value	0.0002	Statistical significant difference
EEL (external elastic lamia)		
Drug coated (Act-D in EVOH)	8.54	0.87
Control (EVOH)	7.94	0.73
p value	0.14	Statistical significant difference

[0138]

	EEL Area (mm^2)				
			Actinomycin		
ID #	Control	ID #	D	ID #	EVOH
48 LCX d	6.3966	63 LCX d	7.4498	63 LAD d	8.3037
48 LCX m	7.4601	63 LCX m	8.2509	63 LAD m	8.8545
48 LCX p	7.3063	63 LCX p	7.7342	63 LAD p	9.4698
49 LAD d	8.5573	63 RCA d	7.9207	64 LCX d	7.8063
49 LAD m	8.5187	63 RCA m	6.9926	64 LCX m	7.1117
49 LAD p	6.6346	63 RCA p	8.3883	64 LCX p	7.2411
58 LAD d	8.6078	65 LAD d	7.8546	64 RCA d	8.3383
58 LAD m	8.1674	65 LAD m	9.2545	64 RCA m	8.0793
58 LAD p	8.3775	65 LAD p	9.2515	64 RCA p	8.3652
59 LCA d	8.3054	68 LAD d	8.7854	65 LCX d	6.4638
59 LCX m	7.3713	68 LAD m	9.5164	65 LCX m	7.1493
59 LCX p	7.8662	68 LAD p	9.1504	65 RCA d	8.5955
59 RCA d	7.3714	69 LCX d	9.6679	65 RCA m	8.0855

-continued

EEL Area (mm^2)

ID #	Control	ID #	Actinomycin D	ID #	EVOH
59 RCA m	6.6783	69 LCX m	9.1237	65 RCA p	8.4785
59 RCA p	7.4707	69 LCX p	9.9849	68 LCX d	8.4723
62 LCX d	7.8784	69 RCA d	9.4765	68 LCX m	7.8382
62 LCX m	7.5318	69 RCA m	7.4424	68 LCX p	8.0570
62 LCX p	6.2647	69 RCA p	9.1462	68 RCA d	8.4840
62 RCA d	8.3240	70 LCX d	8.9504	68 RCA p	8.8767
62 RCA m	7.9535	70 LCX m	8.9117	69 LAD d	6.6648
62 RCA p	8.5454	70 LCX p	8.7533	69 LAD m	6.8614
67 LAD d	8.9532	70 RCA d	7.3249	69 LAD p	7.7632
67 LAD m	9.2410	70 RCA m	7.1061	70 LAD d	7.5175
67 LAD p	8.3841	70 RCA p	8.5830	70 LAD m	7.8630
				70 LAD p	8.2222
AVG	7.8402		8.5425		7.9475
SD	0.8046		0.8755		0.7349

[0139]

ActD vs EVOH	
p =	0.014709
AVG % EEL growth	7.486304

[0140]

IEL Area (mm2)

ID #	Control	ID #	Actinomycin D	ID #	EVOH
48 LCX d	5.2178	63 LCX d	6.3785	63 LAD d	6.9687
48 LCX m	6.2108	63 LCX m	7.5206	63 LAD m	7.3908
48 LCX p	6.1125	63 LCX p	6.9992	63 LAD p	7.3563
49 LAD d	7.2848	63 RCA d	6.9632	64 LCX d	6.4420
49 LAD m	7.4117	63 RCA m	6.0418	64 LCX m	6.0064
49 LAD p	5.9918	63 RCA p	7.4794	64 LCX p	5.9970
58 LAD d	7.2049	65 LAD d	6.2324	64 RCA d	6.800 1
58 LAD m	6.9334	65 LAD m	8.3785	64 RCA m	6.8561
58 LAD p	6.9454	65 LAD p	8.5819	64 RCA p	7.0172
59 LCA d	7.2640	68 LAD d	8.0964	65 LCX d	5.2485
59 LCX m	6.2014	68 LAD m	8.6879	65 LCX m	6.1135
59 LCX p	6.7283	68 LAD p	8.0914	65 RCA d	7.1525
59 RCA d	6.0519	69 LCX d	8.7181	65 RCA m	6.4815
59 RCA m	5.9992	69 LCX m	8.0273	65 RCA p	7.1775
59 RCA p	5.9032	69 LCX p	8.5222	68 LCX d	6.9571
62 LCX d	6.5329	69 RCA d	8.3796	68 LCX m	6.5724
62 LCX m	6.2804	69 RCA m	6.4219	68 LCX p	6.7740
62 LCX p	4.9303	69 RCA p	7.7757	68 RCA d	7.2425
62 RCA d	7.0977	70 LCX d	7.5392	68 RCA p	7.5 554
62 RCA m	6.7466	70 LCX m	7.6573	69 LAD d	5.5505
62 RCA p	7.1747	70 LCX p	6.9749	69 LAD m	5.5571
67 LAD d	8.0264	70 RCA d	6.2815	69 LAD p	6.2697
67 LAD m	8.1144	70 RCA m	5.9760	70 LAD d	6.3212
67 LAD p	7.2091	70 RCA p	7.6195	70 LAD m	6.6518
				70 LAD p	6.9032
AVG	6.6489		7.4727		6.6025
SD	0.7883		0.8972		0.6130

[0141]

ActD vs EVOH	
p =	0.000283
AVG % IEL growth	13.17981

[0142] **FIGS. 7A and 7B** illustrate sample pictures of the histology slides of the coronary vessels from the control group **64** RCA (Right Coronary Group) and the actinomycin D loaded stent group **68** LAD (Left Anterior Descending), respectively. The stent used was an Advanced Cardiovascular Systems Multi-Link Duet™ (stainless steel). As is illustrated by **FIG. 7**B, the positive remodeling of EEL **50**, caused by the application of actinomycin D, creates a gap between stent struts **52** and EEL **50**. Thrombus deposites, illustrated by reference number **54**, are formed in the gap over time. The use of a self-expandable stent eliminates the formation of the gap as the stent self-expands in response to the positive remodeling of IEL. Thrombus deposits can be, accordingly, eliminated.

[0143] Actinomycin D induces the positive remodeling of the vessel walls, more particularly positive remodeling of the external elastic lamina (EEL) of a blood vessel wall. Positive remodeling is generally defined as the ability of the vessel walls to structurally adapt, by increasing in lumen size, to chronic stimuli. A positively remodeled lumen wall has a greater diameter or size as compared to a lumen wall which has not been subjected to the remodeling effect. Accordingly, the flow of blood through the remodeled site is increased—flow which would have otherwise been reduced because of, for example, the presence of plaque build-up or migration and proliferation of cells. The index of remodeling is defined by the ratio of the area circumscribed by the EEL of the lesion site to the area circumscribed by the EEL of a reference site. As a result of the positive remodeling of the EEL, the internal elastic lamina (IEL), in response, can also increases in area or diameter. Actinomycin D, or analogs or derivative thereof, not only can inhibit abnormal or inappropriate migration and/or proliferation of smooth muscle cells, which can lead to restenosis, but can also induce positive remodeling of the blood vessel walls. Thus the widening of the diseased region becomes more pronounced.

Example 27

[0144] 2 grams of an acrylate terminated urethane (Henkel 12892) can be added to 18 grams of ethyl acetate with 0.08 grams of benzophenone and 0.08 grams of 1-hydroxycyclohexyl phenyl ketone. After application, the stent can be cured for 5 minutes under medium pressure mercury lamp.

Example 28

[0145] For a thermoset system, 1.67 grams of Epon 828 (Shell) resin can be added to 98 grams of propylene glycol monomethyl ether and 0.33 grams of Jeffamine T-430 (Huntsman). After application, the stent can be baked for 2 hours at 80° C. and 2 hours at 160° C.

Example 29

[0146] A 0.25% (w/w) solution of tetra-n-butyl titanate can be made in anhydrous ethyl acetate. The solution can be applied by spraying to a surface of a stainless steel stent. The stent can be heated at 100° C. for two hours.

[0147] While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that changes and modifications can be made without departing from this invention in its broader aspects and, therefore, the appended claims are to encompass within their scope all such changes and modifications as fall within the true spirit and scope of this invention.

Example 30

[0148] Objective

[0149] Coated stents tested through simulated delivery to a target lesion for testing the mechanical integrity of the coating.

Group	Quantity	Coating
A	2	Control: 2% EVAL in 1:1 THF: DMSO, 3:1 EVAL: Act-d; no primer
B	2	2% EVAL in 5:3:2 THF:DMF:DMSO, 3:1 EVAL: Act-d; no primer
C	2	EVAL primer layer baked at 120 C/60 C for 2/10 hrs + 2% EVAL in 1:1 THF:DMSO, 3:1 EVAL: Act-d; primer
D	2	EVAL primer layer baked at 140 C/60 C for 2/2 hrs + 2% EVAL in 1:1 THF:DMSO, 3:1 EVAL: Act-d; primer

[0150] Background

[0151] In this experiment four different treatment groups were tested through a simulated delivery and use. Number of peel defects at rings **3**, **5**, and **7**, with a peel defect defined as a location on the stent where coating has been removed to expose bare stent or an underlying layer of coating, were observed.

[0152] Materials and Equipment

[0153] 1. 8, 13 mm Solo stents (Available from Guidant Corporation);

[0154] 2. 8, 3.0x30 mm Duet catheters;

[0155] 3. 100% IPA;

[0156] 4. Tominator Stent Crimper S/N 400;

[0157] 5. 7F JL4 guiding catheter;

[0158] 6. 0.014" Balance Middle Weight guide wire;

[0159] 7. Rotating Hemostatic Valve;

[0160] 8. SVS tortuosity tree (2.5 mm lumen tapering to 1.5 mm lumen);

[0161] Preparation

[0162] Crimped the stents onto the catheters using the Tominator crimper and the following conditions: 3 crimps, 65 psi, rotation between crimps.

[0163] Test Procedure

[0164] 1. Performed simulation using heart model having a tortuosity and contained in a tub filled with water:

[0165] a. Inserted the stents through the following set-up: RHF, 7F JL4 guiding catheter, SVS tortuosity tree (2.5 mm lumen at entrance, 1.5 mm lumen at exit).

[0166] b. Once the stent passed through the distal opening of tortuosity, the balloon was cut from the catheter just distal to proximal marker.

[0167] 2. Examined the stents under 100x magnification using Leica MZFLIII microscope in the clean environment room (CER).

[0168] 3. Recorded number of peel defects at stent rings **3**, **5**, and **7**. Only the OD was examined for peel defects.

[0169] 4. All test samples were handled with personal protective equipment (PPE) appropriate for drug containing stents.

[0170] Data Summary and Results

Group	# Peel Defects/Ring	Comments
A (THF)	2.0	—
B (DMF)	5.3	Began with poor coating finish.
C (140° C.)	0.7	—
D (120° C.)	0	—

[0171] Discussion

[0172] The test was performed to observe the coating integrity after a simulated delivery to a tortuosity without a lesion. The primer layer improved coating adhesion to the stents that resulted in fewer defects after a simulated use. Group B had a number defects. Although the coating surface for Group B was poor to begin with, and the defects were not too severe.

Example 31

[0173] Objective

[0174] The adhesion of 0.67% Actinomycin-D (in 5% EVAL 1:1 THF:DMSO solution) coating on stents with two different surface treatments was compared to control samples. The specific surface treatments consisted of: (1) Argon plasma treatment; and (2) Argon plasma treatment with a primer layer of 5% EVAL in 1:1 DMSO:DMF solution applied with the dip-spin process, i.e., centrifugation process, and followed by heat treatments at 120° C. for two hours and 60° C. for 10 hours. The test method used to test adhesion of coatings on stents was a wet flow test, expanding the stents in a Tecoflex tubing at 37° C. of water or saline. Water or saline is then flushed through the stents for 18 hours to simulate blood flow through the stents. The stents were then removed from the Tecoflex with a "stent catcher" and observed under optical microscope for defects.

Group	Treatment	Flow Rate
A	None	50 mL/min
B	Argon plasma	50 mL/min
C	Argon plasma +5% EVAL in 1:1 DMSO:DMF heated at 120 ° C. for two hours and 60 ° C. for 10 hours	50 mL/min
D	None	100 mL/min
E	Argon plasma	100 mL/min
F	Argon plasma +5% EVAL in 1:1 DMSO:DMF heated at 120 ° C. for two hours and 60 ° C. for 10 hours	100 mL/min

[0175] Materials and Equipment

[0176] 1. 30, 13 mm coated Solo stents, cleaned ultrasonically in IPA for 15 minutes;

[0177] 2. 30, balloon catheters or subassemblies to expand the stents (3.0× 20 mm RX Rocket);

[0178] 3. 0.67% Actinomycin-D in 5% EVAL with 1:1 THF:DMSO solution;

[0179] 4. 5% EVAL in 1:1 DMF:DMSO;

[0180] 5. 3.0 mm, thin walled Tecoflex tubing;

[0181] 6. Saline;

[0182] 7. Lint Free Wipes SU 00126 or equivalent;

[0183] 8. 100% IPA;

[0184] 9. Oven;

[0185] 10. Timer;

[0186] 11. Centrifuge;

[0187] 12. Plasma Machine (available from Advanced Plasma System);

[0188] 13. Ultrasonic cleaner;

[0189] 14. Mettler balance with 0.1 micrograms resolution; and

[0190] 15. Spray Coater with Fan Air Cap and EFD dispenser (EFD Inc. East Providence, R.I.).

[0191] Preparation

[0192] 1. Sonicated the stents in IPA for 15 minutes;

[0193] 2. Weighed each stent to the nearest microgram;

[0194] 3. Prepared 5 stent samples:

[0195] A. Groups A and D:

[0196] i. Performed spray-coating process in CER under the following conditions: 3 passes, 3-second spray, no blowing.

[0197] ii. Weighed each sample at the end of the last pass to the nearest microgram.

[0198] iii. Baked the samples for 4 hrs at 60° C.

[0199] iv. Placed the stents into the Tecoflex tubing with a balloon catheter— submerged in 37° C. saline.

[0200] B. Groups B and E:

[0201] i. Placed the samples on a sample holder. Performed argon plasma treatment using plasma machine.

[0202] ii. Performed spray-coating process in CER under the following conditions: 3 passes, 3-second spray, no blow.

[0203] iii. Weighed each sample at the end of the last pass to the nearest microgram.

[0204] iv. Baked the samples for 4 hrs at 60° C.

[0205] v. Placed the stents into the Tecoflex tubing with the balloon catheter— submerged in 37° C. saline.

[0206] C. Groups C and F:

[0207] i. Placed samples flat on a sample holder. Performed argon plasma treatment.

[0208] ii. Used dip-spin process to apply 2% EVAL primer layer, 1:1 DMSO:DMF.

[0209] iii. Baked the stents at 120°0 C. for two hours.

[0210] iv. Baked the stents at 60° C. for ten hours.

[0211] v. Performed spray-coating process in CER under the following conditions: 3 passes, 3-second spray, no blow.

[0212] vi. Weighed each sample at the end of the last pass to the nearest microgram.

[0213] vii. Baked the samples for 4 hrs at 60° C.

[0214] viii. Placed the stents into the Tecoflex tubing with a balloon catheter— submerged in 37° C. water.

[0215] Test Procedure

[0216] Tested three samples from each group. Wet Flow Testing:

[0217] 1. Expanded the stents into the 3.0 mm Tecoflex tubing in 37° C. saline.

[0218] 2. Performed wet flow testing for 18 hrs.

[0219] 3. Removed the stents from the Tecoflex tubing with a stent catcher.

[0220] 4. Count defects, based on the following categories: Defect type; defect size; defect location; and peel defects on rings **3**, **5**, and **7**.

[0221] 5. Stent weight could not be a measurable because of the loss of the drug and uptake of water.

[0222] 6. All test samples were handled with PPE appropriate for drug containing stents.

[0223] Data Summary

Group	Average # of Peel Defects/ Stent (3 rings) After Flow Test	Average # Peel Defects/ Ring After Flow Test
A	18.0	6.0
B	15.3	5.1
C	2.7	0.9

-continued

Group	Average # of Peel Defects/ Stent (3 rings) After Flow Test	Average # Peel Defects/ Ring After Flow Test
D	14.3	4.8
E	14.0	4.7
F	0.7	0.2

[0224] Discussion

[0225] Peel defects are defined as areas where the coating separated from the stent. The number of peel defects were counted on the stents' OD/sidewall on rings **3, 5,** and **7**. The flow field was on the ID of the stents' surface. Some of the damage to the OD surface could have been aggravated by the Tecoflex tubing. The number of peel defects observed on groups C and F (EVAL primer) was clearly lower than the other two test groups, regardless of flow rate. The increased flow rate did not induce more peel defects.

Example 32

[0226] Objective

[0227] The objective of this experiment was to test the adhesive properties of an Actinomycin-D containing coating on stainless steel stents having an EVAL primer layer. The coated stents were tested in a wet flow test condition of saline heated to 37° C. The number of "peel defects" on a select number of stent rings was observed. A "peel defect" is defined as a location on the stent surface devoid of coating, i.e., bare metal or underlying coating layer that is visible under optical magnification of less than 100×.

Group	Treatment	Flow Rate
A	Argon plasma treatment + EVAL primer layer (15 % EVAL, 1:1 DMF: DMSO) baked at 140° C. for 2 hours and dried at 60° C. for 2 hours	50 mL/min
B Control	Argon plasma treatment + EVAL primer layer (15% EVAL, 1:1 DMF: DMSO) baked at 120° C. for 2 hours and dried at 60° C. for 10 hours	50 mL/min

[0228] Materials and Equipment

[0229] 1. 10, 13 mm Solo stents, cleaned ultrasonically in EPA for 15 minutes;

[0230] 2. 10, balloon catheters or subassemblies to expand the stents;

[0231] 3. 15% EVAL in 1:1 DMF:DMSO solution;

[0232] 4. Actinomycin-D solution, 1:1 THF:DMSO with 3:1 EVAL: Act-D;

[0233] 5. Tecoflex tubing

[0234] 6. Saline

[0235] 7. Lint Free Wipes SU 00126 or equivalent

[0236] 8. 100% IPA

[0237] 9. Oven

[0238] 10. Timer

[0239] 11. Plasma Machine (Advanced Plasma System);

[0240] 12. Ultrasonic cleaner; and

[0241] 13. Mettler balance with 0.1 micrograms resolution.

[0242] Preparation

[0243] 1. Sonicated the stents in IPA for 15 minutes.

[0244] 2. Weighed each stent to the nearest microgram.

[0245] 3. Prepared 5 stent samples for each group:

[0246] A. Group A (Control):

[0247] i. Placed the samples flat on a sample holder. Performed argon plasma treatment.

[0248] ii. Used dip-spin process, i.e., centrifugation at 6000 rpm for one minute, to apply the EVAL primer layer, 1:1 DMSO:DMF.

[0249] iii. Baked the stents at 140° C. for two hours in the convection oven.

[0250] iv. Took weight measurements of each stent to the nearest microgram.

[0251] v. Baked the stents at 60° C. for two hours in vacuum oven.

[0252] vi. Took weight measurements of each stent to the nearest microgram.

[0253] vii. Performed spray-coating process in CER under the following conditions: 3 passes, 3-second spray, no blow.

[0254] viii. Weighed each sample at the end of the last pass to the nearest microgram.

[0255] ix. Baked samples for 4 hrs at 60° C.

[0256] x. Took weight measurements of each stent to the nearest microgram.

[0257] xi. Placed the stents into the Tecoflex tubing with a balloon catheter—submerged in 37° C. water.

[0258] B. Groups B:

[0259] i. Placed samples flat on sample holder. Performed argon plasma treatment.

[0260] ii. Used dip-spin process at 6000 rpm for one minute to apply EVAL primer layer, 1:1 DMSO:DMF.

[0261] iii. Baked the stents at 120° C. for two hours in the convection oven.

[0262] iv. Took weight measurements on each stent to the nearest microgram.

[0263] v. Baked the stents at 60° C. for ten hours in vacuum oven.

[0264] vi. Took weight measurements for each stent to the nearest microgram.

[0265] vii. Performed spray-coating process in CER at the following conditions: 3 passes, 3-second spray, no blow.

[0266] viii. Weighed each sample at the end of the last pass to the nearest microgram.

[0267] ix. Baked the samples for 4 hrs at 60° C.

[0268] x. Took weight measurements of each stent to the nearest microgram.

[0269] xi. Placed the stents into the Tecoflex tubing with a balloon catheter—submerged in 37° C. water.

[0270] Test Procedure

[0271] 1. Performed wet flow testing overnight for about 18 hrs.

[0272] 2. Removed the stents from the Tecoflex tubing with a stent catcher.

[0273] 3. Counted the defects based on the number of peel defects at rings **3, 5,** and **7** on the stents' OD. Count the defects on the ID of the same rings.

[0274] 4. The weight could not be measured because of the loss of the drug and uptake of water.

[0275] 5. All test samples were handled with PPE appropriate for drug containing stents.

[0276] Data Summary and Results

Group	# Peel Defects (OD)	Average # of Peel Defects/Ring (OD, rings 3,5,7)	# Peel Defects (ID)	Average # of Peel Defects/Ring (ID, rings 3,5,7)
A	0	0	1	0.3
	0	0	1	0.3
	0	0	1*	0.3
B	0	0	0	0
	0	0	0	0
	0	0	0	0

*Defect occurred at a location of a defect in the stent surface.

Example 33

[0277] Objective

[0278] The objective of this study was to test the adhesive properties of an Actinomycin-D containing coating on stainless steel stents having an EVAL primer layer. The coated stents were tested under wet flow conditions of saline heated to 37° C. The number of "peel defects" on a select number of stent rings was observed. A "peel defect" is defined as a location on the stent surface devoid of coating, i.e., bare metal or an underlying coating layer that is visible under optical magnification of no more than 100×.

Group	Treatment	Flow Rate
A Control	None	50 mL/min
B	Argon plasma treatment + EVAL primer layer by dip-spin (2% EVAL, 1:1 DMF: DMSO) baked at 140° C. for 4 hours	50 mL/min
C	EVAL primer layer by dip-spin (2% EVAL, 1:1 DMF: DMSO) baked at 140° C. for 4 hours	50 mL/min
D	Argon plasma treatment + EVAL primer layer by spray (2% EVAL, 1:1 DMF: DMSO) baked at 140° C. for 4 hours	50 mL/min
E	EVAL primer layer by spray (2% EVAL, 1:1 DMF: DMSO) baked at 140° C. for 4 hours	50 mL/min

[0279] Materials and Equipment

[0280] 1. 25, 13 mm Solo stents, cleaned ultrasonically in IPA for 15 minutes;

[0281] 2. 25, balloon catheters or subassemblies to expand the stents;

[0282] 3. 2% EVAL in 1:1 DMF:DMSO solution;

[0283] 4. Actinomycin-D solution, 1:1 THF:DMSO with 3:1 EVAL: Act-D;

[0284] 5. 3.0 mm Tecoflex tubing;

[0285] 6. Saline;

[0286] 7. Lint Free Wipes SU 00126 or equivalent;

[0287] 8. 100% IPA;

[0288] 9. Convection Oven

[0289] 10. Timer;

[0290] 11. Plasma Machine;

[0291] 12. Ultrasonic cleaner; and

[0292] 13. Mettler balance with 0.1 micrograms resolution.

[0293] Preparation

[0294] 1. Sonicated the stents in IPA for 15 minutes.

[0295] 2. Weighed each stent to the nearest microgram.

[0296] 3. Prepared 5 stent samples for each group.

[0297] A. Group A (Control):

[0298] i. Performed spray-coating process in CER under the following conditions: 3 passes, 3-second spray, no blow.

[0299] ii. Weighed each sample at the end of the last pass to the nearest microgram.

[0300] iii. Baked the samples for 4 hrs at 60° C.

[0301] iv. Took the weight measurements of each stent to the nearest microgram.

[0302] v. Placed the stents into the Tecoflex tubing with the balloon catheter—submerged in 37° C. water.

[0303] B. Group B:

[0304] i. Placed samples flat on sample holder. Perform argon plasma treatment.

[0305] ii. Used dip-spin process to apply EVAL primer layer, 1:1 DMSO:DMF (6000 rpm for one minute).

[0306] iii. Baked the stents at 140° C. for 4 hours in convection oven.

[0307] iv. Took weight measurements on each stent to the nearest microgram.

[0308] v. Performed spray-coating process in CER at the following conditions: 3 passes, 3-second spray, no blow.

[0309] vi. Weighed each sample at the end of the last pass to the nearest microgram.

[0310] vii. Baked the samples for 4 hrs at 60° C.

[0311] viii. Took the weight measurements of each stent to the nearest microgram.

[0312] ix. Placed the stents into the Tecoflex tubing with a balloon catheter—submerged in 37° C. water.

[0313] C. Group C:

[0314] i. Used dip-spin process to apply EVAL primer layer, 1:1 DMSO:DMF (6000 rpm for one minute).

[0315] ii. Baked the stents at 140° C. for four hours in convection oven.

[0316] iii. Took weight measurements on each stent to the nearest microgram.

[0317] iv. Performed spray-coating process in CER under the following conditions: 3 passes, 3-second spray, no blow.

[0318] v. Weighed each sample at the end of the last pass to the nearest microgram.

[0319] vi. Baked the samples for 4 hrs at 60° C.

[0320] vii. Took weight measurements of each stent to the nearest microgram.

[0321] viii. Placed stents into the Tecoflex tubing with a balloon catheter—submerged in 37° C. water.

[0322] D. Group D:

[0323] i. Placed the samples flat on a sample holder. Perform argon plasma treatment.

[0324] ii. Spray coated primer layer (2% EVAL, 1:1 DMF:DMSO) onto the stents. Used 1.5 sec. spray time, 1-2 passes to achieve 10-40 micrograms of coating.

[0325] iii. Baked the stents at 140° C. for 4 hours in the convection oven.

[0326] iv. Took weight measurements on each stent to the nearest microgram.

[0327] v. Performed spray-coating process in CER at the following conditions: 3 passes, 3-second spray, no blow.

[0328] vi. Weighed each sample at the end of the last pass to the nearest microgram.

[0329] vii. Baked samples for 4 hrs at 60° C.

[0330] viii. Took weight measurements of each stent to the nearest microgram.

[0331] ix. Placed stents into the Tecoflex tubing with a balloon catheter—submerged in 37° C. water.

[0332] E. Group E:

[0333] i. Spray coated primer layer (2% EVAL, 1:1 DMF:DMSO) onto the stents. Used 1.5 sec. spray time, 1-2 passes to achieve 10-40 micrograms of coating.

[0334] ii. Baked the stents at 140° C. for four hours in convection oven.

[0335] iii. Took weight measurements on each stent to the nearest microgram.

[0336] iv. Performed spray-coating process in CER at the following conditions: 3 passes, 3-second spray, no blow.

[0337] v. Weighed each sample at the end of the last pass to the nearest microgram.

[0338] vi. Baked the samples for 4 hrs at 60° C.

[0339] vii. Took weight measurements of each stent to the nearest microgram.

[0340] viii. Placed the stents into the Tecoflex tubing with a balloon catheter—submerged in 37° C. water.

[0341] Test Procedure

[0342] 1. Performed wet flow testing overnight for about 18 hrs.

[0343] 2. Removed stents from the Tecoflex tubing with a stent catcher.

[0344] 3. Counted the defects based on the number of peel defects at rings **1, 3, 5,** and **7** on the stents' OD. Count the defects on the ID of the same rings.

[0345] 4. Stent weight could not be a measurable because of the loss of the drug and uptake of water.

[0346] 5. All test samples were handled with PPE appropriate for drug containing stents.

[0347] Data Summary and Results

Group	Defects/Ring (OD)	Defects/Ring (ID)
Control	2.67	3.00
Dip/Plasma	0.67	0.47
Dip/No Plasma	0.87	0.80
Spray/Plasma	0.47	0.80
Spray/No Plasma	0.67	0.73

[0348] Discussion

[0349] Peel Defects of Primer Coated Stents vs. Untreated Controls

[0350] An improved adhesion, based on the number of peel defects, of the drug containing coating to the Tri-Star stent when an EVAL primer layer was applied is illustrated. All four treatment groups displayed significantly fewer peel defects per stent than the untreated control stents. Use of a spray-coated, 2% EVAL solution in 1:1 DMF:DMSO as a primer significantly improved adhesion of Actinomycin-D containing coating to the Tri-Star stents vs. the controls. The spray-coated primer produced slightly higher peel defect counts compared to the dip-spin deposited primer.

Example 34

[0351] Objective

[0352] The objective of this experiment was to test the adhesive properties of an Actinomycin-D containing coating to stainless steel stents having an EVAL primer layer. More specifically, this experiment attempted to illustrate the effect of different bake times on the final result. The coated stents

were tested under wet flow conditions of saline heated to 37° C. The number of "peel defects" on a select number of stent rings was observed.

Group	Treatment	Flow Rate
A Control	none	50 mL/min
B	Argon plasma treatment + EVAL primer layer by spray (2% EVAL, 1:1 DMF: DMSO) baked at 140° C. for 15 minutes	50 mL/min
C	Argon plasma treatment + EVAL primer layer by spray (2% EVAL, 1:1 DMF: DMSO) baked at 140° C. for 30 minutes	50 mL/min
D	Argon plasma treatment + EVAL primer layer by spray (2% EVAL, 1:1 DMF: DMSO) baked at 140° C. for 60 minutes	50 mL/min
E	Argon plasma treatment + EVAL primer layer by spray (2% EVAL, 1:1 DMF: DMSO) baked at 140° for 120 minutes	50 mL/min

[0353] Materials and Equipment

[0354] 1. 25, 13 mm Solo stents, cleaned ultrasonically in IPA for 15 minutes;

[0355] 2. 25, balloon catheters or subassemblies to expand the stents;

[0356] 3. 2% EVAL in 1:1 DMF:DMSO solution;

[0357] 4. Actinomycin-D solution, 1:1 THF:DMSO with 3:1 EVAL: Act-D;

[0358] 5. 3.0 mm Tecoflex tubing;

[0359] 6. Saline;

[0360] 7. Lint Free Wipes SU 00126 or equivalent;

[0361] 8. 100% IPA;

[0362] 9. Convection Oven;

[0363] 10. Timer;

[0364] 11. Plasma Machine;

[0365] 12. Ultrasonic cleaner; and

[0366] 13. Mettler balance with 0.1 micrograms resolution.

[0367] Preparation

[0368] 1. Sonicated stents in IPA for 15 minutes.

[0369] 2. Weighed each stent to the nearest microgram.

[0370] 3. Prepared 5 stent samples for each group.

[0371] A. Group A (Control):

[0372] i. Performed spray-coating process in CER under the following conditions: 3 passes, 3-second spray, no blow.

[0373] ii. Weighed each sample at the end of the last pass to the nearest microgram.

[0374] iii. Baked the samples for 240 minutes at 50° C.

[0375] iv. Took weight measurements of each stent to the nearest microgram.

[0376] v. Placed the stents into the Tecoflex tubing with a balloon catheter—submerged in 37° C. water.

[0377] B. Group B:

[0378] i. Placed samples flat on sample holder. Perform argon plasma treatment.

[0379] ii. Spray coated primer layer (2% EVAL, 1:1 DMF:DMSO) onto stents. Used 1.5 sec. spray time, 1-2 passes to achieve 10-40 micrograms of coating.

[0380] iii. Baked the stents at 140° C. for 15 minutes in the convection oven.

[0381] iv. Took weight measurements on each stent to the nearest microgram.

[0382] v. Performed spray-coating process in CER under the following conditions: 3 passes, 3-second spray, no blow.

[0383] vi. Weighed each sample at the end of the last pass to the nearest microgram.

[0384] vii. Baked the samples for 240 minutes at 50° C.

[0385] viii. Took weight measurements of each stent to the nearest microgram.

[0386] ix. Placed stents into the Tecoflex tubing with a balloon catheter—submerged in 37° C. water.

[0387] C. Group C:

[0388] i. Placed the samples flat on sample holder. Perform argon plasma treatment.

[0389] ii. Spray coated primer layer (2% EVAL, 1:1 DMF:DMSO) onto stents. Used 1.5 sec. spray time, 1-2 passes to achieve 10-40 micrograms of coating.

[0390] iii. Baked the stents at 140° C. for 30 minutes in the convection oven.

[0391] iv. Took weight measurements on each stent to the nearest microgram.

[0392] v. Performed spray-coating process in CER under the following conditions: 3 passes, 3-second spray, no blow.

[0393] vi. Weighed each sample at the end of the last pass to the nearest microgram.

[0394] vii. Baked the samples for 240 minutes at 50° C.

[0395] viii. Took weight measurements of each stent to the nearest microgram.

[0396] ix. Placed stents into the Tecoflex tubing with a balloon catheter—submerged in 37° C. water.

[0397] D. Group D:

[0398] i. Placed samples flat on sample holder. Perform argon plasma treatment.

[0399] ii. Spray coated primer layer (2% EVAL, 1:1 DMF:DMSO) onto stents. Used 1.5 sec. spray time, 1-2 passes to achieve 10-40 micrograms of coating.

[0400] iii. Baked the stents at 140° C. for 60 minutes in the convection oven.

[0401] iv. Took weight measurements on each stent to the nearest microgram.

[0402] v. Performd spray-coating process in CER under the following conditions: 3 passes, 3-second spray, no blow.

[0403] vi. Weighed each sample at the end of the last pass to the nearest microgram.

[0404] vii. Baked the samples for 240 minutes at 50° C.

[0405] viii. Took weight measurements of each stent to the nearest microgram.

[0406] ix. Placed stents into the Tecoflex tubing with a balloon catheter—submerged in 37° C. water.

[0407] E. Group E:

[0408] i. Placed samples flat on sample holder. Perform argon plasma treatment.

[0409] ii. Spray coated primer layer (2% EVAL, 1:1 DMF:DMSO) onto stents. Used 1.5 sec. spray time, 1-2 passes to achieve 10-40 micrograms of coating.

[0410] iii. Baked the stents at 140° C. for 120 minutes in the convection oven.

[0411] iv. Took weight measurements on each stent to the nearest microgram.

[0412] v. Performed spray-coating process in CER at the following conditions: 3 passes, 3-second spray, no blow.

[0413] vi. Weighed each sample at the end of the last pass to the nearest microgram.

[0414] vii. Baked samples for 240 minutes at 50° C.

[0415] viii. Took weight measurements of each stent to the nearest microgram.

[0416] ix. Placed stent into the Tecoflex tube with balloon catheter— submerged in 37° C. water.

[0417] Test Procedure

[0418] 1. Performed wet flow testing overnight for about 18 hrs.

[0419] 2. Removed the stents from the Tecoflex tubing with a stent catcher.

[0420] 3. Counted the defects based on the number of peel defects at rings **3**, **5**, and **7** on the stents' OD. Count the defects on the ID of the same rings.

[0421] 4. Stent weight could not be a measurable because of the loss of the drug and uptake of water.

[0422] 5. All test samples were handled with PPE appropriate for drug containing stents.

[0423] Data Summary and Results

Group	Total Defects per Stent
Control	3.33
15 min bake	1.00
30 min bake	3.00
60 min bake	1.67
120 min bake	1.33

[0424] Discussion

[0425] The control group with no primer layer had significantly more peel defects as compared to the treatment groups with a primer layer. The groups with shorter baking times (15 and 30 minutes) had higher defect counts than the groups with longer baking times.

Example 35

[0426] Objective

[0427] The objective of this experiment was to test the adhesive properties of an Actinomycin-D containing coating on stainless steel stents having an EVAL primer layer. More specifically, different solvent systems (e.g., THF and DMF) were evaluated. The coated stents were tested under wet flow conditions of saline heated to 37° C. The number of "peel defects" on a select number of stent rings was observed.

Group	Treatment	Flow Rate
A Control	none	50 mL/min
B	Argon plasma treatment + EVAL primer layer by spray (2% EVAL, 1:1 DMF:DMSO) baked at 140° C. for 15 minutes	50 mL/min
C	Argon plasma treatment + EVAL primer layer by spray (2% EVAL, 1:1 DMF:DMSO) baked at 140° C. for 60 minutes	50 mL/min
D	Argon plasma treatment + EVAL primer layer by spray (2% EVAL, 1:1 DMF:DMSO) baked at 140° C. for 240 minutes	50 mL/min
E	Argon plasma treatment + EVAL primer layer by spray (2% EVAL, 1:1 THF:DMSO) baked at 140° C. for 60 minutes	50 mL/min

[0428] Materials and Equipment

[0429] 1. 25, 13 mm Solo stents, cleaned ultrasonically in IPA for 15 minutes;

[0430] 2. 25, balloon catheters or subassemblies to expand the stents;

[0431] 3. 2% EVAL in 1:1 DMF:DMSO solution;

[0432] 4. 2% EVAL in 1:1 THF:DMSO solution;

[0433] 5. Actinomycin-D solution, 1:1 THF:DMSO with 3:1 EVAL: Act-D, 2% EVAL;

[0434] 6. 3.0 mm Tecoflex tubing;

[0435] 7. Saline;

[0436] 8. Lint Free Wipes SU 00126 or equivalent;

[0437] 9. 100% EPA;

[0438] 10. Convection Oven;

[0439] 11. Timer;

[0440] 12. Plasma Machine;

[0441] 13. Ultrasonic cleaner; and

[0442] 14. Mettler balance with 0.1 micrograms resolution.

[0443] Preparation

[0444] 1. Sonicated stents in IPA for 15 minutes.

[0445] 2. Weighed each stent to the nearest microgram.

[0446] 3. Prepared 5 stent samples for each group.

[0447] A. Group A (Control):

[0448] i. Performed spray-coating process in CER under the following conditions: 3 passes, 3-second spray, no blow.

[0449] ii. Weighed each sample at the end of the last pass to the nearest microgram.

[0450] iii. Baked samples for 240 minutes at 50° C.

[0451] iv. Took weight measurements of each stent to the nearest microgram.

[0452] v. Placed the stents into the Tecoflex tubing with a balloon catheter—submerged in 37° C. water.

[0453] B. Group B:

[0454] i. Placed samples flat on a sample holder. Performed argon plasma treatment.

[0455] ii. Spray coated the primer layer (2% EVAL, 1:1 DMF:DMSO) onto the stents. Used 1.5 sec. spray time, 1-2 passes to achieve 10-40 micrograms of coating.

[0456] iii. Baked the stents at 140° C. for 15 minutes in the convection oven.

[0457] iv. Took weight measurements of each stent to the nearest microgram.

[0458] v. Performed spray-coating process in CER under the following conditions: 3 passes, 3-second spray, no blow.

[0459] vi. Weighed each sample at the end of the last pass to the nearest microgram.

[0460] vii. Baked the samples for 240 minutes at 50° C.

[0461] viii. Took weight measurements of each stent to the nearest microgram.

[0462] ix. Placed the stents into the Tecoflex tubing with a balloon catheter—submerged in 37° C. water.

[0463] C. Group C:

[0464] i. Placed samples flat on a sample holder. Performed argon plasma treatment.

[0465] ii. Spray coated the primer layer (2% EVAL, 1:1 DMF:DMSO) onto the stents. Used 1.5 sec. spray time, 1-2 passes to achieve 10-40 micrograms of coating.

[0466] iii. Baked the stents at 140° C. for 60 minutes in the convection oven.

[0467] iv. Took weight measurements of each stent to the nearest microgram.

[0468] v. Performed spray-coating process in CER under the following conditions: 3 passes, 3-second spray, no blow.

[0469] vi. Weighed each sample at the end of the last pass to the nearest microgram.

[0470] vii. Baked the samples for 240 minutes at 50° C.

[0471] viii. Took weight measurements of each stent to the nearest microgram.

[0472] ix. Placed the stents into the Tecoflex tubing with a balloon catheter—submerged in 37° C. water.

[0473] D. Group D:

[0474] i. Placed samples on flat on a sample holder. Performed argon plasma treatment.

[0475] ii. Spray coated the primer layer (2% EVAL, 1:1 DMF:DMSO) onto the stents. Used 1.5 sec. spray time, 1-2 passes to achieve 10-40 micrograms of coating.

[0476] iii. Baked the stents at 140° C. for 240 minutes in the convection oven.

[0477] iv. Took weight measurements of each stent to the nearest microgram.

[0478] v. Performed spray-coating process in CER at the following conditions: 3 passes, 3-second spray, no blow.

[0479] vi. Weighed each sample at the end of the last pass to the nearest microgram.

[0480] vii. Baked the samples for 240 minutes at 50° C.

[0481] viii. Took weight measurements of each stent to the nearest microgram.

[0482] ix. Placed the stents into the Tecoflex tubing with a balloon catheter—submerged in 37° C. water.

[0483] E. Group E:

[0484] i. Placed samples flat on a sample holder. Perform argon plasma treatment.

[0485] ii. Spray coated the primer layer (2% EVAL, 1:1 THF:DMSO) onto the stents. Used 1.5 sec. spray time, 1-2 passes to achieve 10-40 micrograms of coating.

[0486] iii. Baked the stents at 140° C. for 60 minutes in the convection oven.

[0487] iv. Took weight measurements of each stent to the nearest microgram.

[0488] v. Performed spray-coating process in CER under the following conditions: 3 passes, 3 second spray, no blow.

[0489] vi. Weighed each sample at the end of the last pass to the nearest microgram.

[0490] vii. Baked the samples for 240 minutes at 50° C.

[0491] viii. Took weight measurements of each stent to the nearest microgram.

[0492] ix. Placed the stents into the Tecoflex tubing with a balloon catheter—submerged in 37° C. water.

[0493] Test Procedure

[0494] 1. Performed wet flow testing overnight for about 18 hrs.

[0495] 2. Removed the stents from the Tecoflex tubing with a stent catcher.

[0496] 3. Counted the defects, based on the number of peel defects at rings **3**, **5**, and **7** on the stents' OD. Counted defects on the ID of the same rings.

[0497] 4. The weight of the stents could not be a measurable because of the loss of the drug and uptake of water.

[0498] 5. All test samples were handled with PPE appropriate for drug containing stents.

Data Summary and Results

Group	Total Defects per Stent
No primer control	0.00
15 min. bake	0.00
60 min. bake	0.33
240 min. bake	0.00
THF, 15 min. bake	0.00

Example 36

[0499] Objective

[0500] The objective of this experiment was to test the adhesive properties of an Actinomycin-D containing coating on stainless steel stents having an EVAL primer layer made from a DMSO:THF solution applied to the stents. The coated stents were tested under wet flow conditions of saline heated to 37° C. The number of "peel defects" on a select number of stent rings was observed.

Group	Treatment	Drying Time (min.)
A	Argon plasma treatment + EVAL primer	15
B	Argon plasma treatment + EVAL primer	30
C	Argon plasma treatment + EVAL primer	60
D	Argon plasma treatment + EVAL primer	90
E	Argon plasma treatment + EVAL primer	120

[0501] Materials and Equipment

[0502] 1. 10, 13 mm SOLO stents, cleaned ultrasonically in IPA for 15 minutes;

[0503] 2. 2% EVAL in 1:1 THF:DMSO solution;

[0504] 3. 10 Balloon catheters or subassemblies to expand the stents;

[0505] 4. Actinomycin-D solution, 1:1 THF:DMSO with 1:3 Act-D:EVAL, 2% EVAL;

[0506] 5. 4.0 mm Tecoflex tubing;

[0507] 6. Saline;

[0508] 7. Lint Free Wipes SU 00126 or equivalent;

[0509] 8. 100% IPA;

[0510] 9. Convection Oven;

[0511] 10. Timer;

[0512] 11. Plasma Machine;

[0513] 12. Ultrasonic cleaner;

[0514] 13. Mettler balance with 0.1 microgram resolution;

[0515] 14. Spray/bake mandrels and tips;

[0516] 15. Flow Meter, N1429;

[0517] 16. Microscope, minimum magnification 50x;

[0518] 17. EFD controller with spray apparatus without translational stage; and

[0519] 18. EFD controller with spray apparatus with translational stage.

[0520] Preparation

[0521] 1. Sonicated the stents in IPA for 15 minutes.

[0522] 2. Weighed each stent to the nearest microgram.

[0523] 3. Prepare the stent samples for each group.

[0524] A. Primer Coat

[0525] i. Placed samples on sample holder. Performed argon plasma treatment.

[0526] ii. Sprayed the primer layer (2% EVAL, 1:1 THF:DMSO) onto the stents with translational spray coater. Used 1.5 sec. for the spray time and speed **7** to achieve 10-40 μg of coating.

[0527] iii. Baked the stents at 140° C. for the specified time in the convection oven.

[0528] iv. Weighed the stents and recorded measurements to the nearest microgram.

[0529] B. Drug Coat

[0530] i. Sprayed the stents with a 3:1, EVAL:Act-D, 2% EVAL, 1:1 DMSO:THF solution for three seconds per pass for three passes. After each spray pass, dried the stents in the convection oven for 15 minutes at 50° C.

[0531] ii. Weighed the stents and recorded measurements. If the drug coat weight matched the target weight, the stents were returned to the oven for 240 minutes. If weight gain did not match, the stents were returned to the glove box for additional spray coat application. Spray time on subsequent passes was adjusted to achieve target weight.

[0532] 4. Wet Flow Test Sample Preparation

[0533] A. Crimped the stents onto the balloon catheters.

[0534] B. Inflated the stents to 4.0 mm in the Tecoflex tubing with the balloon catheters—submerged in 37° C. water.

[0535] C. Disposed Act-D contaminated water as hazardous waste.

[0536] Test Method/Procedure

[0537] 1. Set flow rate at 50 ml/min.

[0538] 2. Performed wet flow testing overnight for about 18 hrs.

[0539] 3. Removed the stents from the Tecoflex tubing with a stent catcher.

[0540] 4. Counted defects, based on the number of peel defects at rings **1, 3, 5, 7,** and on the stents' OD. Counted defects on the ID of the same rings.

[0541] 5. All test samples were handled with PPE appropriate for drug containing stents.

Data Summary and Results

Drying Time (min.)	Total Defects per Stent	Total Defects per Stent (end rings)	Total Defects per Stent (middle rings)
15	0.0	0.0	0.0
30	2.0	2.0	0.0
60	1.0	1.0	0.0
90	0.0	0.0	0.0
120	0.5	0.5	0.0

[0542] While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that changes and modifications can be made without departing from this invention in its broader aspects and, therefore, the appended claims are to encompass within their scope all such changes and modifications as fall within the true spirit and scope of this invention.

What is claimed is:

1. A method of forming a coating for an implantable device, comprising the acts of:

forming a primer on at least a portion of a surface of the implantable device; and

forming a reservoir region containing an active ingredient on at least a selected portion of the primer.

2. A coating for an implantable device produced in accordance with the method of claim 1.

3. The method of claim 1, wherein the primer provides an adhesive tie layer between the surface of the implantable device and the reservoir region.

4. The method of claim 1, additionally comprising

forming a barrier layer on at least a selected portion of the reservoir region to reduce the rate at which the active ingredient is released from the reservoir region.

5. The method of claim 1, wherein the act of forming the primer comprises:

applying a composition to a selected portion of the surface of the implantable device wherein the composition comprises a thermoplastic polymer added to a solvent; and

heating the composition applied to the selected portion of the surface of the implantable device to a temperature greater than about the glass transition temperature and less than about the melting temperature of the thermoplastic polymer to form the primer.

6. The method of claim 1, wherein the act of forming the primer comprises:

applying a composition to a selected portion of the surface of the implantable device, wherein the composition comprises an inorganic polymer precursor added to a solvent; and

removing the solvent to a significant elimination to form the primer.

7. The method of claim 1, wherein the act of forming a primer comprises:

applying a composition to a selected portion of the surface of the implantable device, wherein the composition comprises a polymer added to a solvent; and

heating the composition applied to the selected portion of the surface of the implantable device to a temperature above the glass transition temperature of the polymer.

8. The method of claim 1, wherein the act of forming a primer comprises:

applying a composition to a selected portion of the surface of the implantable device, wherein the composition comprises a prepolymer and an initiator;

exposing the composition applied to the selected portion of the surface of the implantable device to a condition which polymerizes the prepolymer.

9. The method of claim 8, wherein the condition is exposure to UV radiation.

10. The method of claim 8, wherein the condition is exposure to a selected temperature.

11. The method of claim 1, wherein the primer is made from an ethylene vinyl alcohol copolymer.

12. The method of claim 1, wherein the reservoir region is made from an ethylene vinyl alcohol copolymer.

13. A prosthesis comprising a coating for delivery of an active ingredient, wherein the coating includes:

a reservoir region containing an active ingredient; and

a primer region free from any active ingredients located between the reservoir region and the surface of the prosthesis.

14. The prosthesis of claim 13, wherein the prosthesis is selected from a group of balloon-expandable stents and self-expandable stents.

15. The prosthesis of claim 13, wherein the coating is made from an ethylene vinyl alcohol copolymer.

16. The prosthesis of claim 13, wherein the primer region increases the ability of the coating to be retained by the prosthesis.

17. The prosthesis of claim 13, wherein the primer region acts as an intermediary tie layer between a metallic surface of the prosthesis and the polymeric material from which the reservoir region is made.

18. The prosthesis of claim 13, wherein the primer region is made form a first polymeric layer and the reservoir region is made from a second polymeric layer, the second polymeric layer being made from a different polymeric material than the first polymeric layer.

19. The prosthesis of claim 13, wherein the active ingredient is selected from a group of actinomycin D, paclitaxel and docetaxel.

20. The prosthesis of claim 13, wherein the active ingredient inhibits abnormal or inappropriate migration or proliferation of vascular smooth muscle cells.

21. The prosthesis of claim 13, additionally including a barrier region located on at lease a selected portion of the reservoir region for reducing the rate at which the active ingredient is released.

22. The prosthesis of claim 21, wherein the barrier layer is made from a polymeric material containing inorganic particles.

23. The prosthesis of claim 13, wherein the primer region is made from a material selected from a group of polyisocyanates, unsaturated polymers, high amine content polymers, acrylates, polymers containing a high content of hydrogen bonding groups, and inorganic polymers.

24. The prosthesis of claim 23, wherein the polyisocyanates are selected from a group of triisocyanurate, alphatic polyisocyanate resins based on hexamethylene diisocyanate, aromatic polyisocyanate prepolymers based on diphenylmethane diisocyanate, polyisocyanate polyether polyurethanes based on diphenylmethane diisocyanate, polymeric isocyanates based on toluene diisocyanate, polymethylene polyphenyl isocyanate, and polyester polyurethanes.

25. The prosthesis of claim 23, wherein the unsaturated polymers are selected from a group of polyester diacrylates, polycaprolactone diacrylates, polyester diacrylates, polytetramethylene glycol diacrylate, polyacrylates with at least two acrylate groups, polyacrylated polyurethanes, and triacrylates.

26. The prosthesis of claim 23, wherein the amine content polymers are selected from a group of polyethyleneamine, polyallylamine, and polylysine.

27. The prosthesis of claim 23, wherein the acrylates are selected from a group of copolymers of ethyl acrylate, methyl acrylate, butyl methacrylate, methacrylic acid, acrylic acid, and cyanoacrylates.

28. The prosthesis of claim 23, wherein the polymers containing hydrogen bonding groups are selected from a group of polyethylene-co-polyvinyl alcohol, epoxy polymers based on the diglycidylether of bisphenol A with amine crosslinking agents, epoxy polymers cured by polyols and lewis acid catalysts, epoxy phenolics, epoxy-polysulfides, ethylene vinyl acetate, melamine formaldehydes, polyvinylalcohol-co-vinyl acetate polymers, resorcinol-formaldehydes, urea-formaldehydes, polyvinylbutyral, polyvinylacetate, alkyd polyester resins, acrylic acid modified ethylene vinyl acetate polymers, methacrylic acid modified ethylene vinyl acetate polymers, acrylic acid modified ethylene acrylate polymers, methacrylic acid modified ethylene acrylate polymers, anhydride modified ethylene acrylate coppolymers, and anhydride modified ethylene vinyl acetate polymers.

29. The prosthesis of claim 23, wherein the inorganic polymers are selected from a group of silane coupling agents, titanates, and zirconates.

30. The prosthesis of claim 29, wherein the silane coupling agents are selected from a group of 3-aminopropyltriethoxysilane and (3-glydidoxypropyl) methyldiethoxysilane.

31. The prosthesis of claim 29, wherein the titanates are selected from a group of tetra-iso-propyl titanate and tetra-n-butyl titanate.

32. The prosthesis of claim 29, wherein the zirconates are selected from a group of n-propyl zirconate and n-butyl zirconate.

33. A coating for a stent comprising a first active ingredient and a second active ingredient, wherein the rate of release of the first active ingredient is slower than the rate of release of the second active ingredient.

34. The coating of claim 33, wherein the coating is made from an ethylene vinyl alcohol copolymer.

35. The coating of claim 33, wherein the coating comprises a first region having a first section containing the first active ingredient and a second section containing the second active ingredient.

36. The coating of claim 33, wherein the coating comprises a first region containing the first and second active ingredients and a second region disposed between the first region and the surface of the stent, wherein the second region acts as an intermediary tie layer.

* * * * *

EXHIBIT E

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,516	11/21/2003	Yiwen Tang	50623.304	3018

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APR 21 2008

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SQUIRE, SANDERS & DEMPSEY

EXAMINER	
ROGERS, JAMES WILLIAM	

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
04/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/719,516	TANG ET AL.	
	Examiner	Art Unit	
	JAMES W. ROGERS	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-8,11-18,20,21,23-25 and 28-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-8,11-18,20-21,23-25 and 28-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/03/2008 has been entered.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4,6-8,11,15,17-18,20-21,23-25,28 and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee (WO 01/21229 A1).

Lee teaches an antimicrobial and anti-inflammatory endovascular stent containing a coating comprised of biodegradable polymers including poly(3-hydroxybutyrate-3-hydroxyvalerate) (3-PHB-Co-3-PHV), polycaprolactone (PCL), polyorthoesters, polyglycolic acids, poly lactic acids and blends and combinations

thereof. See abstract, pag 6 lin 24-29, pag 7 lin 26-31and claims. Regarding applicant's limitation for the glass transition temperature for first polymer, as disclosed within applicants own specification the Tg of pure PCL is -62°C, thus since Lee teaches the use of PCL the claim limitation is considered met. Furthermore the Tg of a polymer is just a measurable property of that polymer, since the polymers of Lee are the same as applicants claimed first polymer and polymer additive the limitation is inherently met, because it is inherent that the same compound will have the same properties. Regarding applicant's limitation that the polymeric additive has a degree of crystallization greater than that of the first polymer, once again since the first polymers and polymeric additives are the same it is inherent that the properties of those polymers including the degree of crystallization will be the same for the same compound or polymer. Also since the process of making the coating for a stent and the polymers are being used for the same intended purpose, the degree of crystallization will inherently be the same. Applicants have not set forth in their claims or within the specification how and why their claimed polymers would have a degree of crystallization different than those same polymers known in the art or that are commercially available. The burden is shifted to applicants to show how the degree of crystallization and Tg for their claimed polymers and polymeric additives are different than those polymers taught by Lee.

Claims 1-3,6-8,11-18,20,23-25,28-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Hossainy et al. (EP 0 970,711 A2, cited previously).

Hossainy teaches a process for providing coated stents, the stent coating can be comprised of a PCL and PGA blend. See abstract, [0022], [0025], [0029]-[0031]. The

coating could be a top coating applied to delay the release of a pharmaceutical agent or the coating can be used as a matrix for the delivery of a pharmaceutically active material. Regarding the limitations on the degree of crystallization and the Tg of the first polymer and polymeric additive, the remarks above regarding Lee are incorporated herein, that is since the polymers of Hossainy are the same as applicants claims the examiner assumes the properties of those polymers will inherently be the same. The burden is shifted to applicants to show that the polymers of Hossainy would not have the same claimed properties of applicant's polymers. Regarding claims 12-14 and 29-31 Hossainy teaches that PCL and glycolide could be used in a blend of from about 35:65 to 90:10, within applicants claimed mass ratio.

Claims 1-3,6-8,11,15,17-18,20,23-25,28 and 32 are rejected under 35 U.S.C. 102(e) as being anticipated by DeSimone et al. (US 2004/0181271 A1, cited previously).

DeSimone teaches an intraluminal prosthesis (including stents) comprised of an erodible polymeric material and a coating which can be comprised of PCL, PGA, PLA and the like and blends thereof. See [0028],[0035]-[0037],[0043] and claims 1,36,38 and 39. Pharmacological agents could be incorporated within the stent or within the coating, since the coating can cover a stent containing the active this would meet the limitation in claim 16 in which a topcoat layer is disposed over a drug reservoir layer. Regarding the limitations on the degree of crystallization and the Tg of the first polymer and polymeric additive, the remarks above regarding Lee are incorporated herein, that is since the polymers of DeSimone are the same as applicants claims the examiner assumes the

properties of those polymers will inherently be the same. The burden is shifted to applicants to show that the polymers of DeSimone would not have the same claimed properties of applicant's polymers.

Claims 1-3,6-8,11,15,17-18,20,23-25,28 and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Hossainy et al. (US 2001/0014717 A1, '717 from hereon, cited previously).

'717 teaches a coating for implantable devices (including stents), the coating can be comprised of PCL, PGA, PLA and the like, the T_g of PCL was –60°C. See abstract, [0014],[0034],[0041],[0050]-[0051] and table 3. The polymeric materials were described as being capable of containing an active agent. Regarding the limitations on the degree of crystallization and the Tg of the first polymer and polymeric additive, the remarks above regarding Lee are incorporated herein, that is since the polymers of '717 are the same as applicants claims the examiner assumes the properties of those polymers will inherently be the same. The burden is shifted to applicants to show that the polymers of '717 would not have the same claimed properties of applicant's polymers.

Response to Arguments

Applicant's arguments filed 09/27/2007 have been fully considered but they are not persuasive. Applicants assert that DiSimone, Hossainy and, '717 cannot anticipate their claims because none of the references recite every feature of their claimed invention. Applicants assert that none of the references describe the polymers as having the same Tg or degree of crystallization presently claimed for the first polymer and polymeric additive.

The relevance of these assertions is unclear. As detailed above it is the position of the examiner that since the polymers taught in the references above are the same as applicants claimed polymers (PCL,PLA and PGA) they will inherently have the same properties including Tg and degree of crystallization. Also since the process of making the coating for a stent and the polymers are being used for the same intended purpose, the degree of crystallization will inherently be the same. Applicants have not set forth in their claims or within the specification how their polymers would have a different degree of crystallization and Tg than those same polymers known in the art or that are commercially available. The burden is shifted to applicants to show that the polymers of the references above would not have the same claimed properties of applicant's polymers.

Conclusion

No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James W. Rogers, Ph.D. whose telephone number is (571) 272-7838. The examiner can normally be reached on 9:30-6:00, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Michael G. Hartley/

Supervisory Patent Examiner, Art Unit 1618

Notice of References Cited	Application/Control No. 10/719,516	Applicant(s)/Patent Under Reexamination TANG ET AL.	
	Examiner JAMES W. ROGERS	Art Unit 1618	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N	WO 0121229 A1	03-2001	World Intellect	LEE C C	
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	S. Montserrat et al. Polymer Bulletin 12, 173-180 (1984)
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

EXHIBIT F

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,516	11/21/2003	Yiwen Tang	50623.304	3018

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EXAMINER	
ROGERS, JAMES WILLIAM	
ART UNIT	PAPER NUMBER
1618	
MAIL DATE	DELIVERY MODE
07/02/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/719,516	TANG ET AL.	
	Examiner	Art Unit	
	JAMES W. ROGERS	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-8,11-18,20,21,23-25 and 28-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-8,11-18,20,21,23-25 and 28-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06/08/2009 has been entered.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4,6-8,11,15,17-18,20-21,23-25,28 and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee (WO 01/21229 A1), for the reasons set forth in the office action mailed 04/18/2008.

Claims 1-3,6-8,11-18,20,23-25,28-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Hossainy et al. (EP 0 970,711 A2), for the reasons set forth in the office action mailed 04/18/2008.

Claims 1-3,6-8,11,15,17-18,20,23-25,28,32-34 are rejected under 35 U.S.C. 102(e) as being anticipated by DeSimone et al. (US 2004/0181271 A1), for the reasons set forth in the office action mailed 04/18/2008.

Regarding the new limitations within claims 33-34, DeSimone specifically teaches the use of poly(L-lactide). See [0035] and claims 38-39,73 and 74.

Claims 1-3,6-8,11,15,17-18,20,23-25,28,32-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Hossainy et al. (US 2001/0014717 A1, '717 from hereon), for the reasons set forth in the office action mailed 04/18/2008.

Regarding the new limitations within claims 33-34, Hossainy specifically teaches the use of poly(L-lactide). See [0041], [0051].

Applicant's arguments filed 06/08/2009 have been fully considered but they are not persuasive.

Applicants assert that Lee, DiSimone, Hossainy and, '717 cannot anticipate their claims because none of the references recite every feature of their claimed invention. Applicants assert that none of the references describe the polymers as having the same Tg or degree of crystallization presently claimed for the first polymer and polymeric additive. In order to bolster their argument applicants submitted two references which they purport support their argument that the degree of crystallinity can be different for a

particular polymer and depends upon the conditions under which the polymer was made.

The relevance of these assertions is unclear. As detailed in previous office actions it is the position of the examiner that since the polymers taught in the references above are the same as applicants claimed polymers (PCL,PLA and PGA) they will inherently have the same properties including Tg and degree of crystallization. Applicants have not set forth in their claims or within the specification how their polymers would have a different degree of crystallization and Tg than those same polymers known in the art or that are commercially available. The references presented by applicants do indeed show that polymers with different molecular weights (size) and particle sizes do exhibit different degrees of crystallization, however applicants have not recited within their claims any physical feature of the polymers (MW or particle size) that would exclude the polymers within the references above. The examiner can only search for what is claimed, since the polymers claimed are within the same in scope as what is described in the references above the office assumes that any property derived from those polymers is also necessarily the same. All of the applied references above teach the same coatings comprised of the same polymeric blends as claimed by applicants e.g. PCL and PHB. The polymers disclosed in those references also either recite or inherently teach the same T_g as claimed by applicants. It is well known in the art that the glass transition temperature T_g and the melting temperature T_m of a polymer is inherently linked to it's crystalline structure. See Odian Principles of polymerization pp 24-33, cited previously. Thus it is the position of the examiner that since the polymers

claimed are the same and their T_g values are the same the polymers will inherently have the same degree of crystallization as applicants claimed polymer blend because crystallinity and glass transition temperatures are inherently linked. Also applicants own specification at [0035] of the US PGPUB 20050112171 A1 states "the crystallinity of 3-PHB is about 80% while that of PCL is about 57%" thus as evidenced from applicants own specification it would appear that inherently 3-PHB (described as an additive) has a higher degree of crystallinity then PCL (described as a 1st polymer), thus since all of the above references teach blends of PCL and PHB the limitation is inherently met. It appears as though applicants are trying to claim an undisclosed or unknown property of an old polymeric blend. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case or either anticipation or obviousness has been established, Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-3,6-8,11-15,17-18,20,23-25,28-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hossainy et al. (US 2001/0014717 A1).

Hossainy is described in the previous office action filed 04/18/2008. Hossainey while describing polymeric blends is silent on specific blend ratios. However adjusting

the amounts of biodegradable polymers used as a coating for a stent is clearly a result effective parameter that one of ordinary skill in the art would adjust through routine optimization. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal blend ratio of polymers within a coating by adjusting the blend ratio and types of polymers to find the desired biodegradability of the coating itself and thereby also adjusting the release rate of any active contained within the coating. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of polymer blend ratio within a coating for a stent would have been obvious at the time of Applicant's invention. Furthermore it is noted by the examiner that a ratio of 1:1 is within applicants claimed blend ratios, it would be especially obvious that one of ordinary skill in the art would mix two polymers in a blend in equal amounts of 50:50.

Claims 1-3,6-8,11-15,17-18,20,23-25,28-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeSimone et al. (US 2004/0181271 A1).

DeSimone is described in the previous office action filed 04/18/2008. DeSimone while describing polymeric blends is silent on specific blend ratios. However adjusting the amounts of biodegradable polymers used as a coating for a stent is clearly a result effective parameter that one of ordinary skill in the art would adjust through routine optimization. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the

optimal blend ratio of polymers within a coating by adjusting the blend ratio and types of polymers to find the desired biodegradability for the coating itself and thereby also adjusting the release rate of any active contained within the coating. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of polymer blend ratio within a coating for a stent would have been obvious at the time of Applicant's invention. Furthermore it is noted by the examiner that a ratio of 1:1 is within applicants claimed blend ratios, it would be especially obvious that one of ordinary skill in the art would mix two polymers in a blend in equal amounts of 50:50.

Conclusion

No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James W. Rogers, Ph.D. whose telephone number is (571) 272-7838. The examiner can normally be reached on 9:30-6:00, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Michael G. Hartley/

Supervisory Patent Examiner, Art Unit 1618

RELATED PROCEEDINGS APPENDIX

There are no related proceedings.